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EDITORIALS

The Editor's Progress Report

In this season of holiday cheer an editor does well to count his blessings. With this issue, the Journal completes its second year of publication—an exciting and eventful year which has seen a rapid growth in the stature and scope of the Journal. It has become firmly established as an important scientific publication devoted to clinical cardiology.

The tremendous interest and enthusiasm stimulated by the initial volumes of the Journal have exceeded the most optimistic expectations of the Editorial Board and Publisher. The circulation and subscription lists have approached or surpassed those of other cardiology journals which have been in existence for many years. It is evident that the Journal is fulfilling its function as a medium for postgraduate teaching and as a forum for publication of clinical studies in cardiovascular diseases. It is always gratifying for an editor to find the Journal so widely read and available in so many libraries, hospitals, medical schools and other institutions of higher learning and research.

The need of the Journal is further evidenced by the increasing number of clinicians and investigators from cardiac centers all over the world who have submitted excellent and important manuscripts for publication. These writers have demonstrated their confidence in the Journal as a medium for rapid dissemination of new ideas and information in their particular fields of study. Important reports on new diagnostic methods and advances in therapy are now published fairly rapidly. In fact, in several instances where speed of publication was deemed important, it has been accomplished in one to three months. And yet, in order to reduce the waiting period prior to publication even more, plans have been made to enlarge the size of the Journal.

The Editorial Board has attempted to adhere to the originally proposed program of frequent symposia, seminars and reviews on timely topics and the exhaustive treatment of various subjects in one or more issues of the Journal. Thus, the two volumes of the past year have included symposia and seminars on a wide range of subjects including phonocardiography, ballistocardiography, electrocardiography, peripheral vascular diseases, WPW syndrome, cardiac surgery, diuretic therapy, treatment of hypertension and cardiac arrhythmias. Now in preparation are symposia on pericarditis, catecholamines, electrolytes, space and aviation cardiology, the heart in anesthesia, rehabilitation of the cardiac and various congenital heart lesions.

The great strides which the Journal has made could not have resulted from one man's efforts alone but from the wholehearted and devoted help of all those on the editorial and publication staffs of the Journal and the Publications Committee of the American College of Cardiology. The College has supported the activities of the Journal unwaveringly and in turn the growth of the Journal as its official organ has contributed to the development of the College as an important influence in American cardiology.

I am particularly indebted to the Associate and Assistant Editors who have given unstintingly of their vision, time and energy, to my highly competent Managing Editor and her devoted staff, to the various Guest and Section Editors and to the numerous authors who have contributed to the Journal. To all these and to all readers of the Journal, I extend my sincere thanks and best wishes for a happy Christmas and New Year. With your continued support, I shall continue my efforts to maintain the high standards and prestige of the Journal.

SIMON DACK, M.D.

Why an Encyclopedia of Cardiology?

The recent publication of "Cardiology—An Encyclopedia of the Cardiovascular System" has probably raised in the minds of some physicians and scientists a basic question: Why publish an encyclopedia, i.e., a work of great scope, certainly encompassing a great number of topics, when dealing with cardiology, which is a "subspeciality," a branch of internal medicine?

I shall try to give an answer to this question. In order to do so, I will attempt to explain the present status of cardiology as a "science," a "field of interest," a "field of research" or a "branch of medicine." This will require at the same time the presentation of the philosophy which led to the creation of "Cardiology"—the book.

The Birth of Cardiology

Cardiology, as a branch of the scientific disciplines, was prepared in the sixteenth and seventeenth centuries by the efforts of a score of anatomists, pathologists and physiologists, who described the structure of the cardiovascular system, its main functions and its most common alterations. Their revered names belong to the "golden book" of medicine: Vesalius, Harvey, Vieussens, Lancisi, Morgagni and Malpighi are only a few of the most outstanding.

Between 1750 and 1910, three groups of researchers further advanced the borders of cardiology. Some were great clinicians (Corvisart, Laënnec, Skoda, Auenbrugger, Heberden, Durozier, Potain, Traube); some were physiologists (Ludwig, Marey, Bowditch, François-Frank, Engelmann, Gaskell and many others); others were pathologists (Rokitansky, Virchow, Cohnheim, Kent, Aschoff, Mönckeberg, Talalajeff, Anitschkow and Schottmüller, to quote only some of the best known). However, even in the first few years of the twentieth century, cardiology was not recognized as a separate entity; clinical cardiologists, like MacKenzie, Osler, Wenckebach, Libman or Herrick called themselves "internists;" physiologic cardiologists, like Straub, Hering, Einthoven, Starling, Hürthle or Tigerstedt, called themselves "physiologists;" and pathologic cardiologists, like Aschoff, Tawara or Sternberg, simply thought that they were dealing with certain problems of pathology which chiefly involved the cardiovascular system.

The first definite specialization took place, consciously or unconsciously, when the names of some of the aforementioned scientists or their pupils became synonymous with their work in the field of cardiology and when they or others published textbooks which were devoted either to cardiology or to some of its aspects and became definite landmarks in cardiology.

Among clinicians, Vaquez, Lian, Pezzi, Laubry, Edens; among physiologists, Tigerstedt, O. Frank, Wiggers, Wilson and Katz; among pathologists, Gould, Saphir, Edwards and Lev, thus became identified as "cardiologists." Monographs of electrocardiography, from Codina Altés to Sodi-Pallares and Lepeschkin; of graphic methods, from Lewis to Wenckebach, Weber and Luisada; of roentgenology, from Zdansky to Roesler and Schwedel; and many others dealing with more specialized fields, have identified their authors as "cardiologists." On the other hand, "cardiac surgeons," like Gross, Crafoord, Brock, Blalock, Dogliotti, Harken, Bailey and Lillehei, do not refuse to be called "cardiologists," either in a surgical or in a broader sense.

Current Trends

Several trends exist in modern medicine in regard to cardiology: their contradictions reflect some of the difficulties which are present when one tries to systematize any branch of learning.

(*A*) *Cardiology Is a Laboratory Method Which Helps the "Clinician":* This trend is reflected by appointments in and organization of many hospitals. The cardiologist of the hospital is an internist who reads the electrocardiograms and advises the clinician about fine points of interpretation of these tracings. It is obvious that this narrow point of view is dictated by professional interests and cannot assume great importance. Actually, in most hospitals, a latent tug of war often occurs between the "clinical cardiologist" and "the cardiologist."

(*B*) *Cardiology Is a Branch of Internal Medicine:* This trend, which receives the approval of the Certification Boards (cardiology = subspecialty of internal medicine), excludes large fields which are of interest to the cardiologist.

Physiology, biochemistry, pharmacology and pathology are partly excluded; roentgenology, ballistocardiography, phonocardiography, vectorcardiography, etc., are accepted only as subsidiary or ancillary disciplines or technics, and, therefore, are incompletely known; pediatrics and surgery are considered as allied branches, not as overlapping essential fields. These are only a few examples which could easily be duplicated and amplified.

(*C*) *Cardiology Is Either a Branch of Internal Medicine or of Physiology:* This view varies according to the training, interest and activities of a research worker. This trend is partly followed by the National Heart Institute, which has appointed either physiologists or clinicians as "heart coordinators" in charge of either undergraduate or postgraduate training grants. Distinguished examples of the former group are Oppenheim (Philadelphia, Pa.), Guyton (Jackson, Miss.) and Hamilton (Augusta, Ga.). A "heart coordinator" is also supposed to correlate, promote and increase the teaching of cardiology in the various departments of a medical school, be they physiology or neurology, surgery or psychiatry, pathology or pediatrics. Thus, the outlook of the National Heart Institute is actually far broader and more eclectic than indicated here.

A similar trend is also encouraged by the American Heart Association and by the American College of Cardiology. The American Heart Association gives research grants to physiologists, pathologists and clinicians. It has appointed in the past as its Presidents a physiologist (L. N. Katz) and an experimental pathologist (I. H. Page) and has now as Medical Director another distinguished physiologist (G. Wakerlin). The American College of Cardiology had as Presidents a physiologist (B. Kisch) and an experimental pathologist (G. Meneely) and has bestowed the distinction of honorary fellowship on distinguished physiologists, pharmacologists and pathologists (G. Fulton, H. Goldblatt, W. F. Hamilton, O. Loewi, C. J. Wiggers), while many "pure" researchers are at present in its ranks.

(*D*) *The Broader Outlook:* This admits that cardiology cuts vertically and horizontally across all other disciplines:* it feeds in the classic grounds of anatomy, histology, physiology, pathology and bacteriology; it develops in the main field of internal medicine, including "chest diseases," but also spreads across pediatrics, surgery and anesthesiology; it requires knowledge of extremely technical methods, including ballistocardiography, phonocardiography, vectorcardiography, electro- and roentgenkymography; it uses biochemical technics; it invades the fields of electronics and physics. I have accepted this trend which has been the basis for the creation of the "Encyclopedia of The Cardiovascular System."

* Due to an explosive growth of medical knowledge, this trend is common to other fields (like endocrinology, gastroenterology, diabetes, cancerology, etc.) which were formerly considered as integral parts of internal medicine. This trend has been accepted in surgery, where urology, gynecology, ophthalmology, etc., are now independent branches of the main tree.

Books on Cardiology

Each book on cardiology was the expression of the philosophy of its author. Vaquez's and Eden's works on cardiology had a pathologic-clinical background. White's book on cardiology revealed a pathologic and historic outlook in its first edition. The physiologic-clinical background and the value of graphic methods were stressed by Luisada. In contrast, Levine's and Friedberg's books on cardiology were mostly clinical in approach.

These partial and individual outlooks are necessarily due to two facts: (1) the impossibility for one person to master all the ramifications of cardiology, and (2) the reluctance of publishers to increase the size of these books beyond a certain limit.

When the American College of Cardiology (through its President, Ashton Graybiel) asked me to prepare and edit an encyclopedia of cardiology, the previous considerations were thoroughly discussed at various meetings of the Board of Trustees of the College until finally the widest scope for the work was accepted. It is fortunate that an enlightened and farsighted trend found its expression in the cordial support of the Blakiston Division of the McGraw-Hill Book Company, which accepted to undertake the publication of the "Encyclopedia." This, plus generous grants from five pharmaceutical companies (Burroughs Wellcome, Ciba, Sandoz, Searle and Upjohn), made the creation of "Cardiology" possible.

Structure of the Encyclopedia

This work is composed of five volumes, entitled: (1) Normal Heart and Vessels; (2) Methods in Cardiology; (3) Clinical Cardiology; (4) Clinical Cardiology—Therapy; (5) Related Fields. With the exception of Volume 5 (which will be published in 1960), the

work has appeared in 1959, about four years from the time it was conceived.

Twenty-seven parts or sections comprise the book covering the major disciplines. The importance of embryology and anatomy on one side, and of physiology and biochemistry on the other, explains why Volume 1 is devoted exclusively to these basic foundations of cardiology.

The ever-increasing multiplicity of methods of examination of a patient has required an entire volume (Volume 2) for description, from physical examination to the most technical branches of laboratory studies.

Congenital, rheumatic, bacterial, syphilitic and coronary heart diseases are described in Volume 3, together with the arrhythmias.

Hypertension, hypotension, shock and cor pulmonale; diseases of the large and small vessels; miscellaneous and borderline conditions; heart failure and pulmonary edema; and prevention, management and rehabilitation of the cardiovascular patient are discussed in Volume 4.

Volume 5 will include pharmacology; obstetric, surgical, pediatric and geriatric problems; the cardiovascular patient in the world; effects of environment and physical exertion (including aviation and space cardiology); the past, present and future of cardiology; and the heart of animals.

Cardiology is developing and changing at a very rapid rate. No book can hope to be up-to-date for more than a year or two because writing and publication already entail a minimum of three to four years. For this reason, "Cardiology" was conceived as a loose-leaf work. Each part has separate numbering of pages, tables and figures. Additional or revised chapters will be published periodically, thus keeping the treatise in line with progress of knowledge.

The Authors

The entire work is composed of 326 chapters written by 277 authors and their co-authors. A guiding principle has been the selection of the authors on the basis of their specialty, as follows: anatomists: twelve; physiologists: thirty-nine; pharmacologists: twenty.

Electrocardiography and vectorcardiography are discussed by Barker, Bellet, Benchimol, Grant, Grishman, Holzmann, Johnston, Lepeschkin, Massie, Scherf, Sodi-Pallares and Ziegler.

Phonocardiography and other graphic methods are discussed by Calo, Dressler, Gillick, Luisada and Nadas. Catheterization is described by Björk, Fishman, Gasul, Gorlin, Lynfield and Wood.

Roentgenology, roentgenkymography and angiocardiography are discussed by Castellanos, Cignolini, Cossio, Engle, Fleischner, Heim de Balsac, Schwedel and Steinberg.

Pathologic problems are discussed by Blumenthal, Costa, Fetter, Fisher, Gore, Hildebrand, Koletsky, Lev, Lippschutz, Popper, Rose, Saphir, Spain, Taylor and Tedeschi. Well known pediatricians contributed to "Cardiology" including Blumenthal, Christian, Gasul, Nadas, Robinson and Ziegler.

The group of clinical cardiologists includes Abramson, Crumpton, Dack, Diehl, Elias, Evans, Friedberg, Harrison, Lian, Likoff, Mack, Massey, Moia, Nylin, Priest, Routier, Sigler, Snapper and a score of others.

Cardiac surgeons and anesthetists include Baffes, Bailey, Dennis, Harken, Hufnagel, Julian, Lam, Lynn, Sadove, Scannell, Thompson and Vineberg.

Psychologic, psychiatric and social problems are discussed by Aceves, Cardon, Hellerstein, Josselyn, Miller, Robbins, Wolf, and Zaks.

Science knows no borders or limitations. Even though the majority of the authors are from the United States and Canada, several known scientists from all over the world have contributed to the encyclopedia. Their countries are Argentina, Belgium, Brazil, Cuba, Denmark, East Africa, France, Germany, Great Britain, Greece, India, Ireland, Israel, Italy, Japan, Mexico, Peru, the Philippines, Sweden, Switzerland and Uruguay. Other countries, including Austria, China, Hungary, Poland and Russia, are the countries of origin of authors who now live in the United States, Canada or Great Britain.

Conclusion

Cardiology is a branch of the biologic and medical disciplines, which encompasses physiology, pathology and internal medicine but makes use, or spreads across the borders, of several other "specialties." Information dealing with the structure, function and diseases of the cardiovascular system, as well as with therapy and related fields, can be presented only in an encyclopedic work, authored by various specialists and kept up-to-date through a loose-leaf system. This is the philosophy which led to the creation of "Cardiology"—the book.

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Studies in Hypertension

Stress As an Etiologic Factor in Essential Hypertension*

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THE kidney, the adrenal cortex and medulla, certain enzymes, hepatic factors, trace metals, various humoral agents and salt and water metabolism have all been implicated in the etiology of essential hypertension. While the evidence is adequate to support the participation of one or more of these factors in various hypertensive states, the evidence is not clear as to the nature of the initiating or precipitating factor in patients with essential hypertension. Experimentally such changes are initiated by the investigator, but what factors lead to the development of non-nephritic renal ischemia, adrenal secretory abnormalities, abnormal metabolism of sodium and water, increased vascular sensitivity or abnormal secretion of humoral hypertensive substances in naturally occurring essential hypertension? Examination of the physiologic and metabolic responses to various types of stress suggests a way in which such changes could be initiated, and experimental evidence has already been obtained to indicate that hypertension can be maintained, even though the initiating factor is no longer operating.

EFFECTS OF STRESS ON BLOOD PRESSURE

These effects have been documented in several studies. Experimentally in animals, psychic stress may cause hypertension; in one study, emotional excitement induced in cats by hostile dogs led to hypertension in 50 per cent of the animals. This was associated with cardiac hypertrophy and slight evidence of renal damage.[1]

Imhof et al.[2] presented normal and hypertensive subjects with a series of mathematical tests and also had the subjects speak on topics relative to themselves. Blood pressure was temporarily increased in the majority although in many the rise was small and transient. Hypertensive patients reacted qualitatively like the normotensive subjects but the response was greater. It was also of interest to note that the intensity and duration of the response increased with age, since there is an increasing incidence of hypertension in older age groups. These observations were interpreted to indicate that adaptive mechanisms were slowed in older persons.

Other workers have also noted the effects of psychic stress or stressful interviews in normal and hypertensive patients.[3–10] Hypertensive responses were correlated to psychic responses in which the subject felt menaced or trapped and were due to increased peripheral vascular resistance with a normal stroke volume and pulse rate as in patients with essential hypertension; if on the other hand subjects were overwhelmed, blood pressure tended to fall.[9] These observations were compatible with analyzed personality patterns of hypertensive subjects who were noted to be "mobilized for combat," but who did not or could not take action. Moses et al.[11] noted that rage and resentment were the predominant psychologic manifestations of patients with severe hypertension (blood pressure >160/100 mm. Hg). Subjects with minimal hypertension had anxiety syndromes with minimal overt expression and had the same although less marked alterations in cardiovascular hemodynamics.

In support of their theories, three patients

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were observed in whom malignant hypertension suddenly developed in relation to "major catastrophic events." These patients had spent years in successfully developing their vocation, but failed to be promoted in terms of security, money and position. This led to enragement and a feeling of being trapped, and presumably to the onset of hypertension.

That so-called "labile hypertension," commonly observed to result from mild to severe emotional crises, is often followed by sustained essential hypertension is amply shown by the studies of Levy et al.[12] Their analysis of case records of military personnel revealed that during the period of observation only 2 per cent of originally normotensive patients eventually had sustained hypertension, whereas in 31 per cent of those having "transient hypertension" (blood pressure of 150/90 or greater with subsequent normal values) a sustained elevation of their blood pressure developed. Subjects in whom sustained hypertension developed appeared to be clinically indistinguishable from those with essential hypertension and in some classic cardiovascular-renal complications developed during the period of observation.

More persistent "transient hypertension" has also been observed due to stress. Of 695 men exposed to the stress of combat[13] diastolic hypertension occurred in 27 per cent (diastolic pressure greater than 100 mm. Hg). This persisted in some subjects as long as one to two months after leaving the combat zone. Ruskin et al.[14] noted diastolic pressures greater than 95 mm. Hg in 57 per cent of victims of the Texas City disaster. In his patients elevations persisted for one to two weeks after the stressful stimulation.

In further support of the role of emotional or cortical stimuli in the pathogenesis of hypertension are the occasional observations that psychotherapy,[11] topectomy,[15] leucotomy[16] and lobotomy,[17] may convert patients from a hypertensive to a normotensive state when the procedure results in a change in the patient's mental attitude. Indeed, to anyone who has had experience in the treatment of patients with hypertension, the effects of emotional stress are well known, and all agree that such stimuli are capable of causing further elevations in blood pressure.

Case Reports

Case 1. Mrs. M. C. The patient whose blood pressures are presented in Figure 1 had severe malignant hypertension when first seen. The hypertensive state was controlled during the first year with hexamethonium and later by a combination of hexamethonium and alseroxylon. During the second year it became possible to decrease the dose of hexamethonium and finally to discontinue it; after the thirtieth month all antihypertensive drug therapy was stopped. During the next year and a half blood pressure remained at the upper limits of normal. At this time

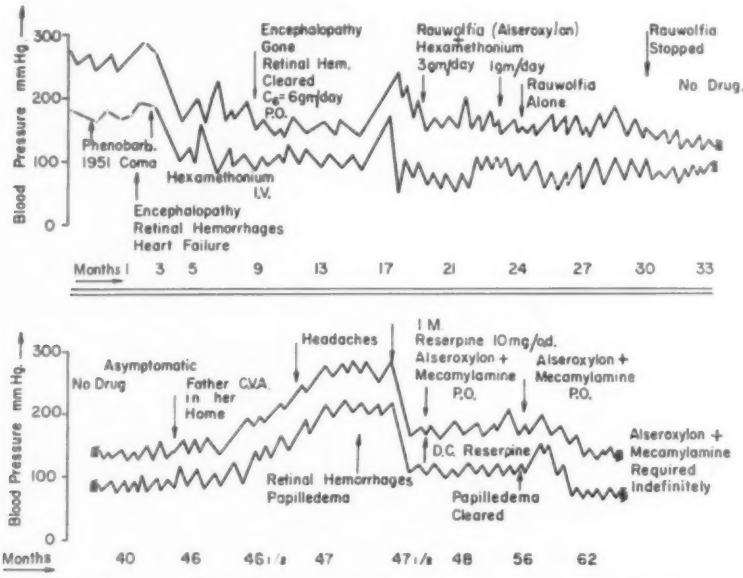

Fig. 1. Case 1. Recurrence of severe hypertension after emotional stress (death of father following a cerebrovascular accident) in a patient previously controlled with drug therapy.

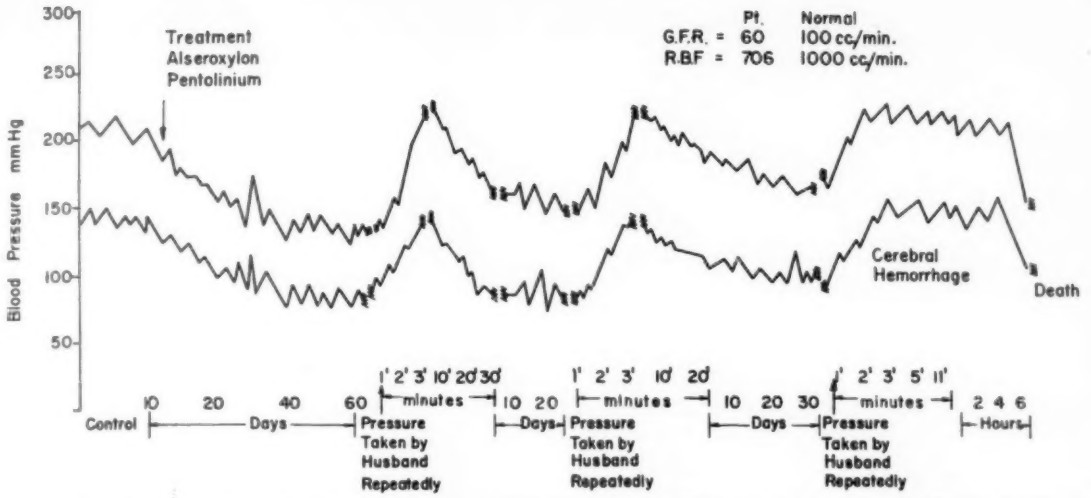

FIG. 2. Case 2. The effect of emotional stress on blood pressure, resulting eventually in cerebral hemorrhage and death. Emotional stress was precipitated by taking of blood pressure by husband.

the patient's father had a cerebrovascular accident. The patient was closely attached emotionally to her father and was noted to be more than usually distressed after this event. In the succeeding few weeks her blood pressure rapidly increased to levels averaging 290/230 mm. Hg. This was associated with retinal hemorrhages, papilledema and headaches. Although it was possible to control the hypertension again with drug therapy, it has not been possible to discontinue it, even though treatment has been continued for over two years. While the recurrence of hypertension may have been coincidental with the father's illness, close observation of this patient's course and emotional situation over a seven-year period suggests strongly that the emotional stress was the precipitating factor.

Case 2. Mrs. R. T. The direct effects of emotional stress on the blood pressure of another patient are presented in Figure 2. She had moderately severe hypertension averaging 205/140 mm. Hg during an initial control period. During therapy with a ganglionic blocking agent and alseroxylon the blood pressure fell to an average of 135/85. The patient's husband was then instructed in taking the patient's blood pressure at home. This led to considerable emotional stress in the patient, and was associated with marked rises in her blood pressure to levels as high as 225/135 mm. Hg. During one of these epi-

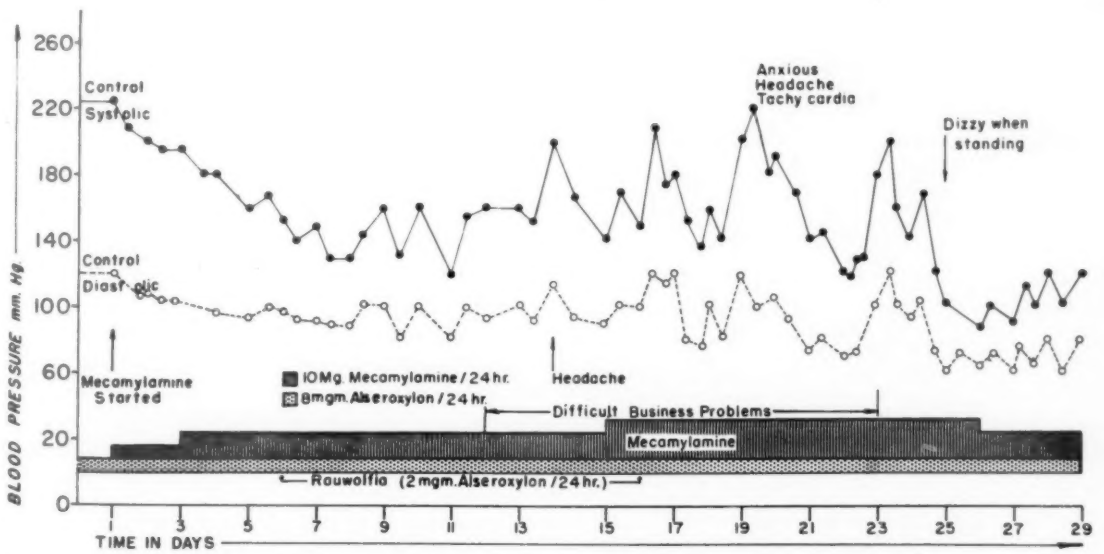

FIG. 3. Case 3. The effect of business problems (emotional stress) on blood pressure. (From: MOYER, J. H. et al. Drug therapy (mecamylamine) of hypertension. *Arch. Int. Med.*, 98: 187, 1956.)

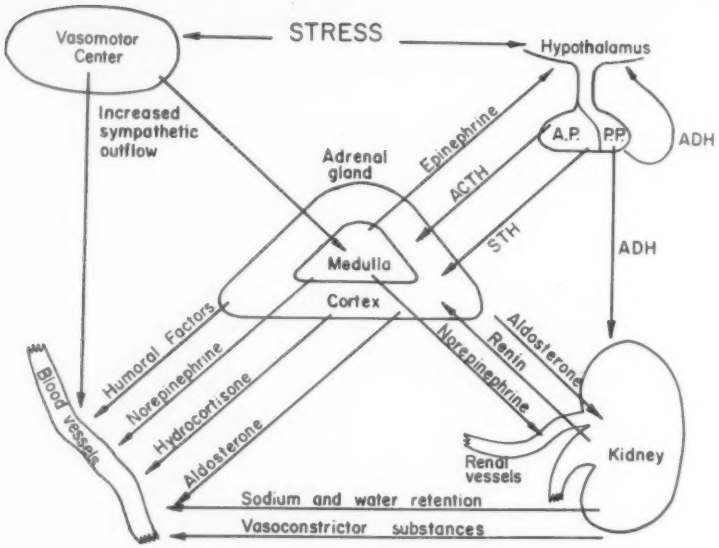

FIG. 4. Mechanisms of hypertensive reactions following stress. See text for discussion.

sodes when the pressure was being taken, the patient had a cerebral hemorrhage and died a few hours later.

Case 3. The blood pressure of a third patient in whom hypertension was aggravated by emotional stress is presented in Figure 3. This patient also had severe hypertension, and failed to respond to rauwolfia therapy alone. With the addition of mecamylamine satisfactory control was obtained (blood pressure averaged 140/95 mm. Hg). At this point he had to cope with difficult business problems for a period of eleven days. During this interval there were rises in blood pressure to levels as high or higher than the pretreatment values, in spite of increased dosage of mecamylamine. When his emotional stress was relieved by solution of his business difficulty, his blood pressure promptly fell to levels of 100/70 mm. Hg with postural dizziness, necessitating reduction of the dose of mecamylamine.

MECHANISMS OF STRESS–INDUCED HYPERTENSION

The data cited clearly indicate that psychic stresses can produce transient hypertension and can aggravate existing essential hypertension. These observations also suggest that such stress may be a primary etiologic factor in at least some patients with essential hypertension. To be explained are the mechanisms by which stress can initiate hypertension and how such an etiology can fit in with the observed abnormalities of essential hypertension. It is well known that emotional stress can effect both the vasomotor centers and the hypothalamic-pituitary axis. As a result of this stimulation a number of potentially hypertensive reactions could be initiated. Some of these are presented in Figure 4.

EFFECTS OF STRESS ON THE AUTONOMIC NERVOUS SYSTEM

The effects on the autonomic nervous system are manifest in response to emotion, trauma and other stimuli. Both parasympathetic and sympathetic functions may be affected depending on the type of stress and results in characteristic and well known manifestations. Those of increased sympathetic function include increased blood pressure and variable changes in cardiac output, stroke volume, pulse rate and peripheral resistance, and this is confirmed by the finding of increased amounts of urinary catecholamines.[18–21]

EFFECTS OF STRESS ON ADRENAL MEDULLARY FUNCTION

Such effects are mediated through the sympathetic nervous system and result in increased secretion of epinephrine and norepinephrine as evidenced by clinical manifestations and increased excretion of these substances in the urine. However, of particular bearing is the evidence that secretion of these two amines is not always in constant proportion.[20,21] This probably accounts for the variations in cardiac output and pulse rate in relation to blood pressure response, cardiac output being increased when epi-

nephrine secretion is predominant and little changed when norepinephrine predominates. Further, the tolerance of pilots to the vascular (and emotional) stress of increased gravity can be correlated with urinary excretion of norepinephrine and epinephrine, high levels of norepinephrine occurring during high "g" tolerance and an aggressive, hostile attitude and increased levels of epinephrine with low tolerance and acute anxiety.[20,21] This response could be modified in the same subject by appropriate "psychotherapy" by the psychiatrist.

These data are of particular interest since they correlates closely with the observed cardiovascular hemodynamic changes produced when various emotional states are induced in normal subjects, i.e., a tendency to increased blood pressure, primarily due to increased vascular resistance when a hostile response was elicited (norepinephrine type response), and tachycardia, increased cardiac output and little change in blood pressure when an anxiety reaction was induced (epinephrine type response). Since small amounts of norepinephrine may cause an elevation of blood pressure with little if any associated clinical signs, this could be an operating factor in beginning essential hypertension.

EFFECTS OF STRESS ON RENAL FUNCTION

Effects on renal function have been studied by several investigators. Injection of India ink into the renal vessels of normal cats and those stressed by confrontation with a barking dog revealed decreased renal cortical circulation in the stressed cats.[22] Electrical stimulation of cerebrocortical pressor areas[23] and painful stimuli[24] have also led to renocortical ischemia.

Emotional stress in normal and hypertensive human subjects may lead to diminished renal blood flow.[6–8] In such instances renal blood flow may decrease to 75 per cent of control values, accompanied by a slight decrease in glomerular filtration rate, and an increase in the filtration fraction and renal vascular resistance. In sympathectomized patients the response was modified; efferent arteriolar constriction did not occur, while afferent arteriolar constriction was unchanged, suggesting that both neurogenic and humoral factors were operating in non-sympathectomized patients. While such renal hemodynamic responses are probably not characteristic of a given stimulus, it is of interest that similar alterations can be produced in man by infusion of norepinephrine (Fig. 5).

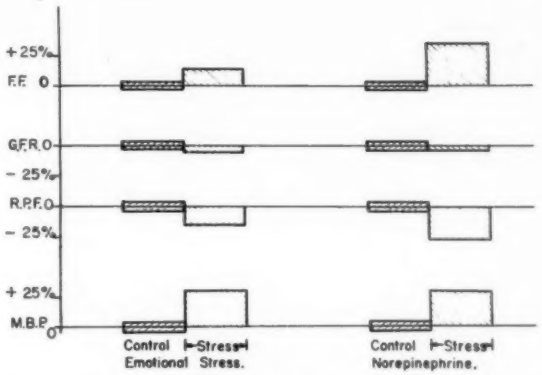

FIG. 5. Comparison of the effects of emotional stress and norepinephrine infusion on renal hemodynamics. F.F. = filtration fraction, G.F.R. = glomerular filtration rate, R.P.F. = renal plasma flow, and M.B.P. = mean blood pressure. Note that changes are qualitatively similar. The data on stress effects were adapted from PFEIFFER J. B., Jr. and WOLFF, H. G. *J. Clin. Invest.*, 29: 1227, 1950.

Stress may also influence urine volume and electrolyte excretion. Unpleasant stimuli[25] and fright due to sounding of an automobile horn[26] have led to antidiuresis in dogs, and Verney[27] has shown that emotional stress may cause release of antidiuretic hormone. Sodium may be retained as a result of both emotional[26] and traumatic stress (bone fracture).[28] In the latter experiment there was increased potassium excretion, probably indicative of adrenal cortical activation.

EFFECTS OF STRESS ON PITUITARY FUNCTION

Effects on pituitary function and therefore presumably on hypothalamic function have been demonstrated. Adrenocorticotropic hormone is released by stress,[29] frustration due to forced restraints being particularly effective.[30] Increased amounts of somatotropin may be released during stress,[31] and as already noted there may be increased release of antidiuretic hormone.[27]

EFFECTS OF STRESS ON ADRENAL FUNCTION

Effects on adrenal function are also well documented. In surgical or traumatic stress[32,33] well marked, easily detectable changes occur. There are large rises in plasma and urinary 17-hydroxycorticoids. Characteristic negative nitrogen balance, retention of sodium and water, potassium excretion and many other metabolic changes occur.

In emotional and psychic stress adrenal activation has been more difficult to demonstrate

and many studies have shown negative results. However, since the development of more refined technics for measuring plasma ACTH, hydrocortisone and urinary corticosteroids, such changes have been demonstrated in response to a number of different types of psychic stress. Urinary 17-ketogenic steroids increased significantly in eight subjects repeating an examination in which an unsatisfactory outcome meant a marked reorientation of their vocational outlook.[34] Urinary 17-hydroxycorticoids were increased in the urine of members of a crew racing team on days of timed practice and the day of the actual race. On days of non-emotionally stressed rowing (i.e., non-timed practice) urinary excretion was not significantly different from days on which no rowing was done,[35] suggesting that psychological stress was the important determinant. Adrenocortical steroids have been noted to increase in response to emotional arousal characterized by anxiety of a disintegrative nature,[36] in students during college exams,[37] in psychiatric patients on admission to a mental hospital,[38] during anxiety,[39] during stressful life experiences,[40] in disturbed schizophrenic subjects and in patients with other mental disorders[37] and in response to frustrating psychological tasks.[41] Such changes in response to emotional stress are often subtle, difficult to detect, and within normal physiological ranges, although when viewed in relationship to suitable control determinations and analyzed statistically they are highly significant.

Comments

The mechanism by which stress may produce or aggravate hypertension is still not completely clear, but as noted there is ample proof that stress of an emotional nature does stimulate the central sympathetic centers, hypothalamus and pituitary. Increased sympathetic activity could lead to direct arteriolar vasoconstriction including the renal arterioles, as well as to stimulation of the adrenal medulla to secrete increased amounts of epinephrine and norepinephrine into the circulation which in turn would cause vasoconstriction. Renal vasoconstriction could lead to renal ischemia with resultant liberation of renin or other vasoconstrictor factors. Renin in turn might act on the adrenal cortex with resultant secretion of additional humoral vasoconstrictor factors or substances increasing vascular sensitivity to vasoconstrictor impulses or humoral agents. Secreted epinephrine, in addition to its vascular effects, may stimulate the hypothalamus and pituitary gland[42] although its role in human hypothalamic-pituitary function is not yet clear.

This stimulation in combination with stimuli descending through cortical hypothalamic or other central pathways as a result of stress could lead to secretion of ACTH which in turn would stimulate adrenal cortical secretion of hydrocortisone and other steroids. This could lead to renal sodium and water retention and perhaps to a sensitization of vascular smooth muscle to vasoconstrictor agents. Secretion of somatotrophin may also be increased; it has been suggested that this may be one factor regulating adrenocortical secretion of aldosterone.[31,43] The latter would tend to increase renal sodium and water retention and might have a direct cellular effect on the ratio of intracellular to extracellular potassium or other electrolytes thereby increasing vascular reactivity. Somatotrophic hormone may also sensitize vascular tissues to the effect of mineralocorticoids.[43] In addition renal damage including nephrosclerotic-like lesions can be produced experimentally by administration of somatotrophin in some way which may not be related to mineralocorticoids but related to adrenal integrity since the damage is prevented by adrenalectomy even though replacement therapy is given.[30] Antidiuretic hormone is also released in stress. This could potentiate water retention.

Conclusions

An analysis of these interrelationships is consistent with much of the data relating to naturally occurring hypertension in man. In addition, it is consistent with the known action of various hypotensive drugs used in the treatment of hypertension. Agents which act centrally, such as hydralazine, diminish sympathetic outflow, while reserpine and chlorpromazine probably decrease sympathetic outflow and reduce hypothalamic-pituitary function. Other agents, such as ganglionic blocking drugs or adrenergic blocking drugs, block the sympathetic nervous system peripherally. Hydralazine may also act by reducing vascular sensitivity locally. Amphenone or aldosterone antagonists block the adrenocortical response locally or at the renal tubular level, and diuretics and sodium restriction counteract the effects of sodium and water retention.

It would seem that if essential hypertension were primarily on the basis of a local renal defect and ischemia, or a renal enzymatic defect leading to increased secretion of renin or other

vasopressor agents, that there would be diminished sympathetic tone and therefore little response to either centrally or peripherally acting sympatholytic drugs. Similar arguments may be advanced if any single peripheral factor is considered as the primary cause.

This suggests that there are multiple abnormalities present in essential hypertension, and that these most likely occur as a result of stimulation of the central nervous system; while any one abnormality might not be of sufficient magnitude to be hypertensive in itself a combination might be synergistic. Such changes would be difficult to detect by conventional laboratory methods and when detected might only be significant when viewed in the light of the total abnormalities; for example as in the case of increased adrenal activity in response to emotional stress, it has only been recently that these changes could be detected. Furthermore, patients classified as having essential hypertension may be a heterogeneous group in which there is a greater sympathetic, hormonal, electrolyte or other abnormality in one patient as compared to another; this would make statistically positive correlations almost impossible. That such a possibility is likely is suggested by the group of patients with essential hypertension reported as having an "endocrine hypertensive syndrome."[44]

Although a convincing case can be made out for the role of stress in the etiology of essential hypertension, the evidence to date is primarily circumstantial (however, no more so than any other suggested etiologic possibility for essential hypertension in man), and much further work is necessary to prove this or any other possibility. However, there is no doubt, as emphasized previously, that emotional stress can and does aggravate existing essential hypertension.

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The Relationship of the Adrenal Cortex to Hypertension*

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As WITH fever and many other manifestations of disease states, hypertension may be due to one or a combination of etiologic agents. In some instances, as is true in patients with a pheochromocytoma, the etiologic mechanism is well understood; in others, and especially in essential hypertension, possible mechanisms have been proposed, but have not yet been clearly established. In these latter instances, experimental and clinical observations suggest that adrenal cortical hormones may be connected intimately with the pathogenesis of hypertension and it is certain that such hormones, if not directly involved, are necessary to, or exert a "permissive" action on, its development and maintenance.

The evidence which suggests that adrenal cortical hormones may be a primary etiologic factor in some types of hypertension is steadily increasing. Such a relationship was perhaps first suspected when hypertension was noted to be one of the major manifestations of Cushing's syndrome. This observation was reinforced when desoxycorticosterone acetate (DCA) was noted to increase blood pressure to normal in patients with Addison's disease, and that further increases in dosage in such patients often led to the development of hypertension. In experiments with animals, using appropriate accompanying conditions, administration of DCA leads to development of severe hypertension, cardiovascular and renal disease. The "pharmacologic" use of cortisone, hydrocortisone, prednisone and fluorohydrocortisone, as well as many other synthetic steroids, is associated with the development of hypertension in a significant number of patients. Other evidence which suggests adrenal participation is (1) the occurrence of hypertension in certain patients with congenital adrenal hyperplasia, (2) its occurrence in some animals after adrenal enucleation during the phase of adrenal regeneration, (3) the possible relationship of hypertension to stress and the "adaptation syndrome," (4) the finding, in some patients and animals, of electrolyte alterations of the type commonly resulting from large doses of adrenal steroids, (5) the hypotensive effect of drugs which block the electrolyte effects of adrenal steroids and (6) the frequent occurrence of clinical syndromes, which although not classic of Cushing's syndrome, are characterized by hypertension plus varying combinations of obesity, diabetes, hirsutism and menstrual disturbances, suggestive of adrenal dysfunction. In addition, adrenalectomy has been shown to lower blood pressure significantly in a large percentage of patients with hypertension.

CUSHING'S SYNDROME

Hypertension is a common finding in Cushing's syndrome, being present to some degree in as much as 85 per cent of patients. When adrenalectomy is performed early in the course of the disease, arterial blood pressure often returns to normal and remains at this level even though adequate replacement therapy with hydrocortisone and desoxycorticosterone acetate is instituted. In those patients with a more advanced state of disease, in whom vascular and renal deterioration has occurred, this procedure may have little effect on the hypertension but undoubtedly secondary factors such as pressor agents from the damaged kidney are responsible for maintenance of elevated blood pressure in this phase of the disease.

The evidence seems clear-cut that in Cushing's syndrome the primary etiologic factor in the hypertension is excessive or unbalanced adrenal

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cortical secretion. On the other hand, it is difficult to determine the exact steroidal abnormality responsible for the hypertension. It is known that secretion of hydrocortisone is increased. Other steroids such as 17-ketosteroids and estrogens are also found to be increased variably. Genest et al.[1] reported aldosterone to be increased markedly in one hypertensive patient with Cushing's syndrome, the daily excretion ranging from 32 to 210 μg. per day (normal values for this method are 1.0 to 9.5 μg.). Another patient who was normotensive excreted 5.3 μg. per day; however, a third patient with moderate hypertension also had normal values of 3.5 and 5.0 μg. per day.

Congenital Adrenal Hyperplasia

In patients with congenital adrenal hyperplasia it is well known that a salt-losing or hypertensive syndrome may be associated with the clinical picture of female pseudohermaphrodism and macrogenitosomia precox. In Wilkin's series[2] five patients with congenital adrenal hyperplasia were hypertensive. In all of these blood pressure returned to normal during therapy with cortisone. In one patient blood pressure became elevated with cessation of therapy and again returned to normal when cortisone was reinstituted. In these patients, as in Cushing's syndrome, hypertension is due to abnormalities of adrenal cortical secretion. A possible mechanism for this was elucidated by Eberlein and Bongiovanni[3] who studied the urinary steroid excretion pattern in one patient who had severe hypertension in association with congenital adrenal hyperplasia. In this patient, 11-oxygenated steroids were undetectable, and the predominate C-21 steroids were tetrahydro-11-desoxycortisol, tetrahydrodesoxycorticosterone, pregnanetetrol and pregnanetriol. Large amounts of etiocholanolone and androsterone were also present. Since 11-desoxycortisol has minimal, if any, hypertensive effects it was postulated that excessive secretion of desoxycorticosterone was the most likely explanation of the hypertension, and that this resulted from a lack of adrenal cortical 11-β-hydroxylase.

In other patients with congenital adrenal hyperplasia, there seems to be a greater deficiency of 21-hydroxylase than of 11-β-hydroxylase[4] with the resultant effect that production of salt-retaining substances may be diminished; in some patients this becomes of sufficient magnitude to result in a salt-losing syndrome with hypotension.

Primary Aldosteronism

Primary aldosteronism is due to excessive secretion of aldosterone by the adrenal cortex, the most common pathologic lesion being a benign adenoma which occurs in 90 per cent of patients. In approximately fifty patients mentioned by Conn[5] the majority had hypertension. In many of these aldosterone has been shown to be the only steroid present in excessive amounts. Removal of the tumor is associated with a return to the normotensive state in most, but not all, of these patients. Even though hypertension continues in a few patients, the significance of these observations is not lessened, since it is likely that those patients not having a hypotensive response after adrenalectomy had developed secondary renal disease (hypokalemic nephrosis), pyelonephritis, or perhaps a situation analogous to experimental DCA hypertension, in which hypertension is permanent if DCA therapy is continued beyond a critical period of time.

In spite of these results, it is somewhat disturbing to note that patients with familial periodic paralysis (intermittent aldosteronism) do not have hypertension[5] but it is possible that chronic elevation of circulating aldosterone with secondary renal disease is necessary for the development of severe hypertension.

Other Types of Adrenal Cortical Hypersecretory States

Hypertension is uncommon in other types of adrenal cortical hypersecretory states. In purely masculinizing syndromes (adrenogenital syndromes in adults) and in patients with feminizing adrenal cortical carcinomas, elevation of blood pressure is not common. These observations suggest that adrenal androgens and estrogens do not play a major role in the development of hypertensive states.

In addition to these syndromes, there are less well defined conditions characterized by Schroeder and Davies as "endocrine hypertensive syndromes."[6] In an analysis of female patients with hypertension in their clinic about 20 per cent were found to have, in addition to hypertension, features suggestive of an endocrine disorder which could be related to possible adrenal or gonadal disturbances. Their symptoms and signs included sudden gain of weight prior to the onset of the hypertension,

development of central obesity and "buffalo hump," reproductive disturbances (most commonly, irregular menses, 74 per cent); a tendency to ecchymoses, 60 per cent; hirsutism, 40 per cent; tendency to edema, 40 per cent; abnormal carbohydrate tolerance, 25 per cent; and acne, 21 per cent. "If all of the findings in these women were consolidated into one case, that case would have Cushing's syndrome without osteoporosis." Some confirmation was lent to the diagnosis by the finding of adenomata or focal hyperplasia of the adrenal cortex in every one of seven patients in whom it was possible to examine the adrenal glands.

Administration of Steroids

Desoxycorticosterone Acetate: Administration of certain adrenal cortical steroids to human subjects and animals leads to the development of hypertension. In normal rats administration of desoxycorticosterone acetate produces mild hypertension. If rats are "sensitized" by unilateral nephrectomy and sodium chloride is added to their drinking water severe hypertension and later severe vascular disease results. It should be noted that this is reversible in the early phases if therapy is stopped, but becomes permanent if vascular disease and renal deterioration are permitted to develop. In normal man DCA administration usually has little effect on blood pressure[7] even in relatively large doses as compared to those required for maintenance of a patient with Addison's disease; but again as in animals, if sodium intake is excessive or renal disease is present the blood pressure effects are potentiated. On the other hand, in patients with adrenal insufficiency it is quite easy to produce hypertension with DCA, suggesting that in the normal subject certain adrenal steroids may have an antagonistic effect to DCA and that the resultant hypertension in patients with Addison's disease is due to the deficiency of steroids having an antagonistic action to DCA rather than the absolute level of desoxycorticosterone alone. DCA also has a pressor effect in hypertensive dogs[8] and in hypertensive patients.[7]

Cortisone and ACTH: Hypertension frequently develops in normotensive patients treated with cortisone and ACTH when large doses are given.[9] Similar results have been achieved with hydrocortisone, prednisone, prednisolone, fluorohydrocortisone and other synthetic steroids with mineralocorticoid activity. The incidence of hypertension can usually be correlated with dosage, but not necessarily with sodium-retaining potency. For example, the incidence of hypertension is approximately the same from hydrocortisone and prednisone when equivalent anti-inflammatory doses are used, even though at these dose levels sodium retention is greater with hydrocortisone. In contrast, administration of ACTH or cortisone to hypertensive patients may not lead to further elevation of blood pressure[10] and it has been reported that in occasional patients blood pressure may decline toward normal during administration of cortisone.[11,12]

Aldosterone: Administration of aldosterone to normal subjects has led to some increase in blood pressure; however, in two subjects large doses (3 mg. and 6 mg./day for fourteen and twenty-two days, respectively) elevated the diastolic pressure only 10 to 20 mm. Hg.[13] This seems analogous to the situation in familial periodic paralysis and it is possible that a longer course of treatment might have led to a greater rise in blood pressure.

Steroid Excretion in Patients with Essential or Renal Hypertension

Reports concerning excretion of steroids in essential and renal hypertension have been variable and conflicting. Genest[14] studied seven patients with essential hypertension for periods of two to seven months under conditions of high and low sodium intakes. Although seven different chromatographic fractions of urinary steroids were examined there was no distinct abnormality in excretion of steroids. During severe sodium restriction five of the patients became normotensive. Repetition of steroid analyses at this time revealed no significant change in the excretion pattern. Tobian[15] found normal formaldehydogenic steroids in eight of nine patients with essential hypertension, and Daughaday[16] in three patients. In contrast, Corcoran et al.[17] noted increased levels in twenty of forty-six patients; in patients in whom four or more determinations were done, urinary formaldehydogenic steroids were elevated in nine of ten. Bioassays of urinary corticoids have also shown increases in some patients with hypertension.[18]

In a series of sixteen women studied at the Hahnemann Hospital Hypertensive Clinic, the mean urinary excretion of 17-hydroxycorticoids and 17-ketosteroids was not significantly different from that of non-hypertensive patients;

however, due to possible variables in race, sex, age, concurrent disease, duration and type of hypertension, a much larger series will be necessary to determine if there are differences in steroid excretion in these two groups of patients. Since steroidal imbalance may be important, determinations of various classes of steroids should be done simultaneously.

Venning et al.[19] measured the excretion of free and conjugated formaldehydogenic steroids glucocorticoids and "sodium retaining factor" in normal pregnant women, in toxemia of pregnancy and in hypertension of pregnancy without toxemia. Glucocorticoids were lower than normal in toxemia; sodium retaining factor, and free and conjugated formaldehydogenic steroids were increased in toxemia and in the hypertensives with the exception that conjugated formaldehydogenic steroids were less than normal in patients with severe toxemia.

Aldosterone Excretion: Genest et al.[1,20] measured excretion of aldosterone in normal control subjects and in fifty-four patients with essential, malignant and renal hypertension. The mean excretion of the hypertensive group was approximately two times normal, 55 per cent of this group having levels above normal or in the high normal range. Marked fluctuations in aldosterone excretion were found in three patients in whom serial determinations were carried out, this also being in contrast to the normotensive subjects. In three patients with hypertension due to coarctation of the aorta, excretion of aldosterone was within normal limits. It should be noted that these studies did not determine whether or not the increased aldosterone excretion was primary or secondary and while the data from patients with coarctation suggest it is not due to the hypertension *per se*, in the hypertension of coarctation, the adrenals, kidneys and liver are not subjected to the effects of the elevated blood pressure and the adrenal response could well be modified.

Steroid Formation in Hypertension: Steroid formation by adrenal tissue from normotensive patients and those with hypertension has been studied *in vitro*. Cooper et al.[21] found that the rate of steroid formation per gram of adrenal cortical tissue declined with increasing diastolic blood pressure. However, this was associated with a fall in the ratio of hydrocortisone/corticosterone due to the fact that formation of corticosterone declined less rapidly than hydrocortisone with increasing levels of diastolic blood pressure. In spite of this the rate of formation of all steroids measured except 11-β-hydroxyandrostene-3,17-dione was doubled in the less severe hypertensive group as compared with the normotensive group. There was a positive correlation between adrenal weight and diastolic blood pressure. It was thought by these authors that the finding of decreased hydrocortisone in relation to corticosterone suggested a possible deficiency of adrenal 17-hydroxylase.

Pathology of the Adrenal Cortex in Hypertension

The pathologic appearance of the adrenal cortex in patients with hypertension has been reported by several authors.[6,21–25] Although the cortex appears to be normal in some patients, pathologic lesions are frequently found. Etienne-Martin[26] noted lymphocytic islets (73 per cent), muscular hyperplasia of the central adrenal vein (73 per cent), spongiocytic hyperplasia (69 per cent), fibrosis of the capsule with arteriolitis and hyalinization (63 per cent) and loss of fibrosis of the zoma glomerulosa (50 per cent) in the adrenal glands of patients with hypertension. The adrenals may be increased in weight and this has been correlated with diastolic blood pressure.[21] Areas of nodular hyperplasia, focal adenomas and arteriosclerosis of adrenal vessels may be present.[6,21–23] Russi observed 131 instances of adrenal adenoma in the records of 9,000 autopsies.[24] Hypertension was five times more common in this group than in those without adenomas. The adenomatous group was further characterized by having less arterial nephrosclerosis than the hypertensive patients without adenomas, suggesting that the hypertension may have had a different etiology.

Although renal vascular involvement was less in Russi's patients, steroid hypertension may be associated with severe vascular disease. Experimentally, the severity and incidence varies with the steroid used, chronic DCA administration being associated with severe vascular disease.[27] In contrast the pathologic change due to DCA administration in dogs can be prevented by administration of adrenal cortical extract[28] and vascular disease is less severe when hypertension is induced by cortisone.[29]

Possible Mechanisms of Steroid Hypertension

The exact pathogenesis of steroid-induced

hypertension is unknown, although several possibilities have been suggested. Since hypertension may be induced experimentally by adding saline to the drinking water of rats[30] and since steroids may lead to salt retention, it has been suggested that this is a likely mechanism.

Electrolyte Effects: Albert et al.[31] have observed significantly higher plasma sodium and significantly lower serum magnesium levels in patients with uncomplicated essential hypertension than in normal control subjects; however, serum potassium levels were not significantly altered. Similar findings have been observed in patients with adrenal cortical hyperactivity. While this finding is suggestive, the electrolyte pattern is not completely typical of that due to steroids since the latter patients are much more likely to have a lowered serum potassium than an elevated serum sodium level. In contrast, Hollander observed that total body sodium (Na^{21} space), total body potassium (K^{42} space) and extracellular fluid volume ($S^{35}O_4$ space) were not altered in patients with essential and renal hypertension as compared to normal controls, while in Cushing's syndrome potassium was decreased and sodium and extracellular fluid volume were normal or increased.[31] Other evidence against steroid hypertension being the result of electrolyte effects is the observation that SC-8109 [Searle 19-nor analog of 3-(3-oxo-17-β-hydroxy-4-adrosten-17-α-yl) propionic acid γ-lactone] may induce sodium diuresis and potassium retention in primary aldosteronism without a fall in blood pressure.[33] On the other hand, SC-6584 [Searle 17α-propyl-4,5-β-dihydro-19 nortosterone] produces a lowering of blood pressure in metacorticoid, perinephritic and adrenal regeneration hypertensive rats and increases sodium excretion.[34] In addition patients with essential hypertension have been found to respond qualitatively the same to the Hickey-Hare test as those with Cushing's syndrome.[35]

Increased Reactivity of Blood Vessels: Hypertension might also result from increased sensitivity of vascular smooth muscle to epinephrine and norepinephrine; this might be induced by a direct steroidal effect on these tissues or by changes in electrolyte concentrations in these tissues.[8] However, recent data[36] indicate that reactivity of blood vessels to epinephrine and norepinephrine, at least in experimental hypertension when aortic strips are tested in *in vitro* assays, is not greater than normal and may even be diminished.

Adrenals, An Intermediary Link in Renal Hypertension: A third way in which the adrenals may be directly involved in the pathogenesis of hypertension is that of an intermediary and essential link in the development of renal hypertension. That there is more than a "permissive" role is suggested clinically by the fact that 80 per cent of patients with severe hypertension are significantly benefited by adrenalectomy plus limited sympathectomy even though receiving steroid replacement therapy[37] and by the fact that certain hypertensive patients in whom Addison's disease develops become hypotensive and although adequate replacement therapy is given (which should be sufficient steroids for a permissive effect), blood pressure is maintained at normotensive levels.[38] This is further supported by the fact that the adrenal cortex is necessary for the development of renoprival hypertension and that adrenalectomy in the nephrectomized partner or parabiotic rats abolishes hypertension in the nephrectomized rat but is not necessary for maintenance of normal blood pressure.[39] In experimental nephrogenic hypertension there is adrenal hypertrophy[8] and the width of the zona glomerulosa is increased by renin.[40,41] On the other hand, Fregly[42] was able to produce hypertension in adrenalectomized rats with latex encapsulation of the kidneys, and it is possibe to maintain renal hypertension in adrenalectomized animals by administration of exogenous steroids.

Permissive Action of Steroids: A fourth possibility is that in essential hypertension secretion of adrenal hormones is normal and that steroids have a permissive action, rather than a direct effect. That is to say that the presence of such hormones is necessary for the biochemical or other reactions responsible for the development of hypertension, but that they do not exert any hypertensive effect in themselves.[5,40]

Imbalance in Steroid Secretion: Finally, it is possible that some patients with hypertension have an imbalance in steroid secretion leading to a disproportion in the amount of one steroid as related to another rather than hypersecretion of a given steroid as is present in Cushing's syndrome. Such a disproportion could be present if the secretion of one steroid was in the low normal range and another in the high normal range; yet in this situation secretion of individual steroids when considered alone would

be normal. Some evidence for this as a possible mechanism is the finding of a disproportionate secretion of corticosterone and hydrocortisone when adrenal glands from hypertensive patients were perfused *in vitro*.[21] Excessive amounts of 11-dehydrocortisol and desoxycorticosterone with undetectable amounts of hydrocortisone have been found in urine extracts from one patient with congenital adrenal hyperplasia and severe hypertension.[3] Corcoran noted that when dogs with renal hypertension were adrenalectomized and given "adequate" replacement therapy with specific hormones, blood pressure was not fully restored to the previous hypertensive level whereas when adrenal cortical extract was given the pressure was restored.[25] Since it is likely that adrenal cortical extract may contain less hydrocortisone in relation to mineralocorticoids than is normally secreted, steroidal imbalance could be a possible explanation in this situation. Hypertension occurs in rats during the regeneration phase following adrenal enucleation.[43] Here again it seems that there could well be disproportionate steroid secretion leading to hypertension.

Thorn et al.[38] reported that progression of vascular disease ceased in hypertensive patients in whom Addison's disease developed. In these patients administration of desoxycorticosterone increased blood pressure to prior levels and vascular disease progressed. However, when cortisone and desoxycorticosterone were combined, patients could be maintained at normotensive levels. This evidence suggests that while hydrocortisone may be hypertensive in itself when given in large doses, physiologic amounts may counteract the hypertensive effects of salt-retaining hormones. In acute experiments in normal control subjects infusion of small amounts of cortisone has been shown to cause sodium excretion whereas larger amounts cause sodium retention.[44] In addition to hydrocortisone other steroids may be secreted which have antagonistic effects to salt-retaining hormones.

Progesterone Deficiency: Progesterone has natriuretic effects in normal subjects but in patients with Addison's disease treated with cortisone alone, natriuresis does not occur; however, if aldosterone is given to the same patient concurrently with cortisone, progesterone then has sodium-excreting effects, suggesting that this compound blocks aldosterone at the renal tubular level. It could be postulated then that a chronic deficiency of such a substance might lead to excessive salt retention and hypertension, although aldosterone secretion is normal. In this regard it is of interest that 74 per cent of Schroeder's patients with the "endocrine hypertensive syndrome" had menstrual disturbances, and all patients had some abnormality of the reproductive system.[6]

Conclusions

It is clear that some well-defined syndromes, certain steroids from either endogenous or exogenous sources result in hypertension. If untreated, all of the cardiovascular and renal complications of so-called essential hypertension may develop in such patients. In these patients, hypertension is usually cured if therapy is instituted before severe vascular complications and resulting initiation of other hypertensive mechanisms ensue. This group includes patients with Cushing's syndrome, congenital adrenal hyperplasia, primary aldosteronism and patients receiving large doses of certain steroids.

In a second ill-defined group of patients, characterized by hypertension, obesity and menstrual disturbances, and with a tendency to hirsutism, edema, acne and impaired carbohydrate tolerance, but in whom a definite diagnosis of adrenal hyperfunction cannot be made using existing criteria, there is a strong suggestion that some hormonal imbalance is the responsible etiologic factor. This is borne out in part by the not infrequent finding of pathologic lesions in the adrenal cortices of such patients. In Schroeder's clinic 20 per cent of all women with hypertension could be placed into this category.

In hypertension known to be primarily due to renal disease, the adrenal glands may play an important secondary role. Although there is little clinical evidence to support this hypothesis, experimental work indicates that under certain circumstances adrenal cortical function must be present for the development of renal hypertension. However, this role may be permissive rather than a direct participating one.

Finally there is a large group of patients with "essential" hypertension. In these patients hypertension can often be abolished by adrenalectomy, and some studies have shown increased urinary excretion of cortical steroids, notably a moderate increase in aldosterone excretion. In addition, adrenal weight can be correlated with the level of diastolic pressure. On the other hand, excretion of steroids has

been normal in many patients with hypertension and it is possible that all of the above observations could be explained on the basis of a permissive role of adrenal hormones and the stress of prolonged hypertension. To be explained are certain electrolyte abnormalities suggestive in some instances of a steroid effect. Certain new synthetic steroids as well as certain normally secreted adrenal steroids have an antagonistic action to salt-retaining corticoids and it may well be that an imbalance between these two groups of steroids is the etiologic factor in a portion of the patients now classified as having "essential" hypertension.

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Epidemiology of Hypertension with Particular Reference to the Bahamas

I. Preliminary Report of Blood Pressures and Review of Possible Etiologic Factors*

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MANY ATTEMPTS have been made during the past thirty years to explain the fact that Negroes in the Unites States apparently have a higher blood pressure in all age groups than whites.[1–6] This difference in blood pressure has been explained as being secondary to economic deprivation, malnutrition, frequency of syphilis in the Negro race or "social and environmental stresses" that accompany any mixed racial society. Comparisons have been drawn repeatedly between studies on the African native that demonstrated lower levels of blood pressure in all ages and both sexes among peoples living in primitive surroundings, and reports from areas where societies have become more complicated, in an effort to link elevation of blood pressure to the "stress" of modern civilization. Unfortunately, most of the studies reported from Africa are from areas near Kenya,[7–9] that were not involved in the slave trade to a great extent, and consequently do not represent data on the ancestors of the American or West Indian Negro. These latter peoples are descendents of the natives of the west coast of Africa; namely Ghana, Liberia, Nigeria and French Equatorial Africa. Reports of blood pressure studies from this area are sparse, although isolated reports from Ghana suggest that blood pressure in the natives rises after "urbanization."[10]

Not all natives living in Africa have low blood pressure, however, and although reliable data are not available, reports from the Belgian Congo suggest that hypertension is not rare in this area.[11] These studies suggest that in natives in primitive surroundings elevated blood pressure does develop and, in some instances, pressure is comparable to that noted in Negroes in the United States. Reports from South Africa also suggest that hypertension is not uncommon among the Bantu and among the Negro population in Capetown, South Africa,[12] and that the severity of the hypertension, both with regard to cardiovascular complications and elevation of diastolic blood pressures, is more pronounced in the Negro than in the whites living in this area. Blood pressure among the Negro females in Capetown is reported to be strikingly higher than among other groups studied, although the incidence of toxemia of pregnancy is not believed to be unusual. Despite the fact that the American and West Indian Negro probably differ considerably from the Capetown and Bantu Negro, the prevalence and severity of hypertension appear to be similar in the two groups.

Reports from the Virgin Islands[13] and Panama[14] indicate that blood pressure levels of the Negro population are higher than in whites, although postmortem studies suggest that a large percentage of cases in Panama may be secondary to renal disease and do not represent cases of primary or essential hypertension.[14]

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TABLE I

Average Blood Pressure (mm. Hg) by Age and Sex in Negro Population—Nassau, The Bahamas

Age (yr.)	Female*		Male*	
	No.	Blood Pressure	No.	Blood Pressure
Under 20	266	122/77	162	120/75
20–24	176	127/79	69	127/77
25–29	135	130/81	71	132/81
30–34	136	138/86	59	135/85
35–39	136	147/90	56	141/86
40–44	106	161/97	90	144/91
45–49	96	166/99	46	144/92
50–54	55	166/96	39	153/94
55–59	40	176/101	27	169/97
60–64	52	185/100	52	166/96

* Total females, 1,198. Total males, 678.

In an effort to clarify the data regarding blood pressure in the Negro race, an epidemiologic study of the disease was initiated in the Bahamas two years ago. This area was chosen for several reasons: (1) There was a suggestion from earlier reports that elevated blood pressure was a common finding.[15,16] (2) The area is divided into several large islands, with mixed white and Negro populations, and hundreds of small Cays or islands with Negro populations only. This allows for comparisons of findings in "urbanized," more "competitive" areas such as Nassau on the island of New Providence, and those on isolated, more primitive islands with just a few inhabitants. (3) Populations are static, especially on the smaller Cays, and total populations may be studied repeatedly. This would eliminate errors of sampling and loss of follow-up in any long term longitudinal investigation. (4) Tropical diseases and malnutrition, factors which may account for the reports of extremely low pressures in African natives, are not prevalent in this area. (5) Preliminary investigations suggested that cooperation of the native population would be excellent in any studies undertaken, since most Bahamians were aware of the frequent occurrence of "the high blood" and "strokes" among their people, and were willing to help in any study or treatment program.

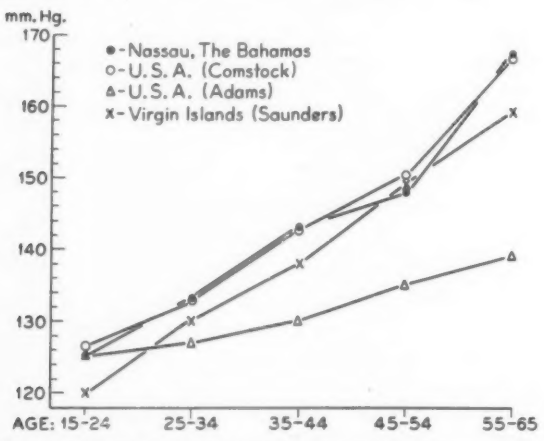

FIG. 1. Mean systolic blood pressures in representative male Negro populations.

Two approaches to the problem of prevalence in the Bahamas were attempted. The first, which forms the basis for this report, represents a study of (1) 1,869 Negroes in Nassau, New Providence, an island with approximately 55,000 white and Negro inhabitants; (2) 1,595 people on Grand Bahama Island, a large island in the northern part of the Bahamas, with a total population of approximately 5,000 Negroes and (3) a study of the total adult Negro population of 130 people on Exuma, a small island to the south of New Providence. The method of selection of these patients is outlined herein.

A second investigation will be reported separately in which a representative sample of 3,500 people on the island of New Providence (Nassau) were studied after being carefully selected according to statistically accepted sampling methods.

Material and Methods

NASSAU, NEW PROVIDENCE

With the aid of physicians both in private practice and at the Princess Margaret Hospital in Nassau, questionnaires, which included basic data on age, sex, weight and height, number of pregnancies, family history with regard to high blood pressure or heart disease, occupation and associated illnesses, were completed on 1,869 Negro male and female residents of this island. Patients were divided into several groups:

(1) A group of consecutive male patients from the private practice of two of the participating physicians.

(2) Patients from the outpatient department of the Princess Margaret Hospital, mainly from the general medical clinics.

(3) A group of female patients followed in the prenatal clinic of the hospital and examined during the first three months of pregnancy.

(4) A group of young male laborers examined for physical fitness prior to embarking to the United States.

Although it was realized that certain obvious sampling errors existed in selecting patients in this

manner, the method of selection was believed to be comparable to the methods employed in other studies previously reported (i.e., factory workers, hospital outpatients, private practice patients) with which the present data were to be compared.

Blood pressure was recorded with a mercury sphygmomanometer with the patient in the sitting position, utilizing the disappearance of sound as the diastolic blood pressure. In approximately one half of the patients multiple readings were recorded and in these cases the average of the several readings was used in recording data. Urinalyses, with the exception of microscopic examination, were performed on 420 patients. In addition, fifty patients with hypertension selected from the original group of hospital outpatients were carefully studied with regard to renal function and cardiovascular changes in an attempt to establish base line data regarding the severity of hypertensive disease. A dietary history was obtained when possible and twenty-four-hour sodium excretion was determined in a limited number of patients.

GRAND BAHAMA ISLAND

Approximately 1,600 people of a total of 5,000 were studied by Dr. Adolf Richter and data similar to that mentioned were recorded. Blood pressure in this group was rounded to the nearest 10 mm. Hg and may, therefore, differ somewhat from the results obtained in the other two groups. No attempt at selection of these patients was made and the records utilized in the study represent the actual patient data obtained by Dr. Richter during his examinations of patients.

ROLLEVILLE EXUMA

The entire adult population of 130 people over the age of twelve years was studied in this community by Dr. Freda Bonner by means of a questionnaire. Urinalyses were performed on all patients in this group.

Results

NASSAU

A summary of blood pressure data on 1,198 females and 671 males is presented in Table I. Mean blood pressure tends to be higher in both sexes with increasing age. Higher systolic and diastolic levels occur in females in most age groups.

Figures 1 to 4 compare mean systolic and diastolic pressures of Negro males and females in several different populations with those in Nassau. Data compared are those of Comstock,[3] who studied individuals in a biracial Georgia, U. S., community; Adams,[1] who investigated blood pressures of male factory workers in New Orleans; and Saunders,[13]

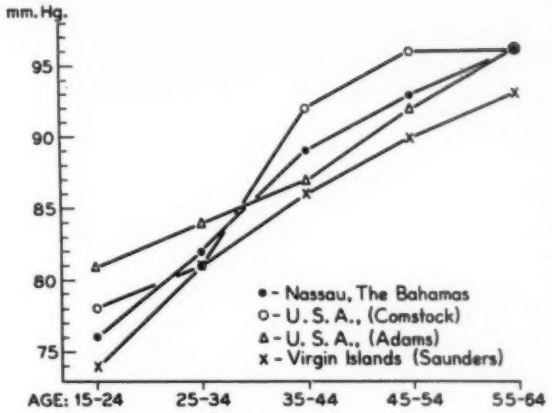

FIG. 2. Mean diastolic blood pressures in representative male Negro populations.

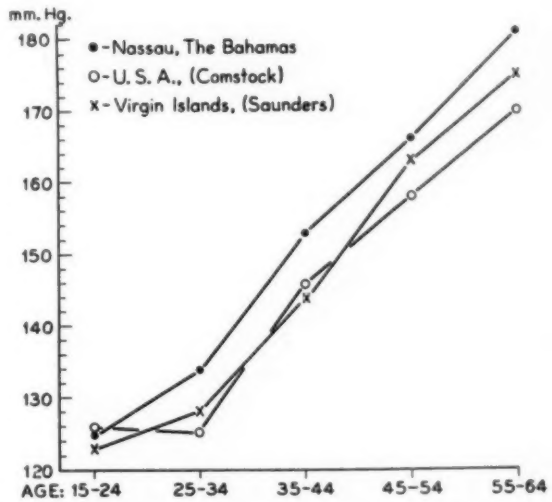

FIG. 3. Mean systolic blood pressures in representative female Negro populations.

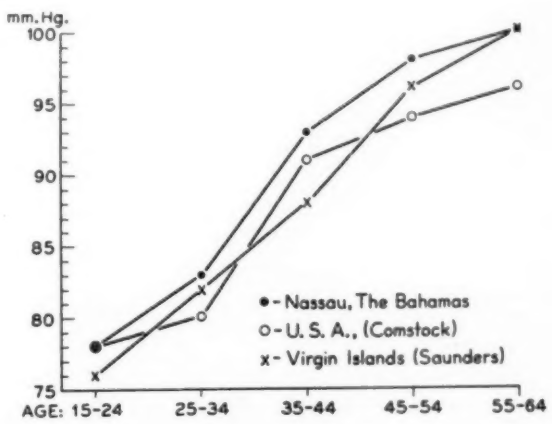

FIG. 4. Mean diastolic blood pressures in representative female Negro populations.

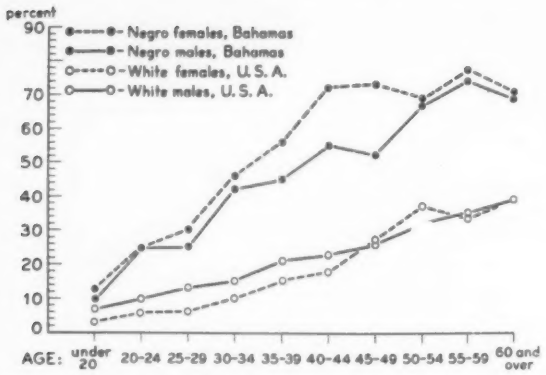

FIG. 5. Per cent of diastolic blood pressures over 90 mm. Hg.

who studied approximately 5,000 Negro inhabitants of the Virgin Islands. Systolic blood pressures in males are quite similar in the Comstock, Virgin Islands and Nassau studies despite the differences in methods of sampling (Fig. 1). Systolic blood pressure levels in the group of factory workers (Adams) were significantly lower than in the other studies, in which subjects with many different occupations were examined.

Diastolic blood pressure in the males as well as both systolic and diastolic levels in females are comparable in the populations compared in Figs. 2, 3 and 4. Blood pressure in the Nassau females is somewhat higher in all age groups.

No attempt was made to define "hypertension" or arbitrarily to divide the population into "hypertensive" subjects.

Over-all percentage of females with a diastolic blood pressure of 100 mm. Hg or over was 24 per cent of the 1,198 females examined; 20 per cent of the males examined had a diastolic

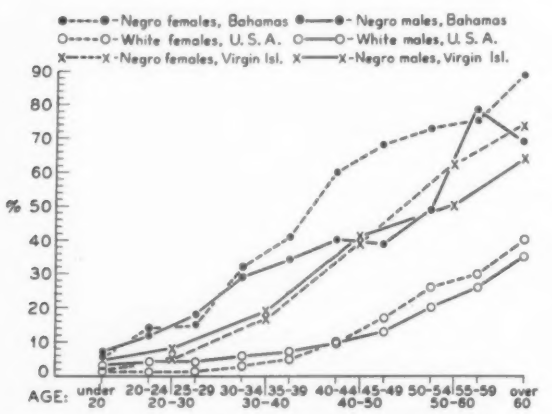
●----●-Negro females, Bahamas ●——●- Negro males, Bahamas
o----o- White females, U. S. A. o——o- White males, U. S. A.
x----x -Negro females, Virgin Isl. x——x -Negro males, Virgin Isl.
90
80
70
60
% 50
40
30
20
10
0
AGE: under 20 20-24 20-30 25-29 30-34 30-40 35-39 40-44 40-50 45-49 50-54 50-60 55-59 over 60

FIG. 6. Per cent of systolic blood pressures over 150 mm. Hg.

blood pressure of 100 mm. Hg or more. As will be noted, the percentage of patients, both male and female, with "elevated" diastolic blood pressures rose steadily with age. Blood pressure of the females was generally higher, however, in all age groups.

Thirty per cent of females and 24 per cent of the males had a blood pressure of 150/90 mm. Hg or higher.

In comparing the blood pressure data obtained in the Bahamas with data on white persons studied by Master[17] in the United States it will be noted (Fig. 5) that the percentage with elevated diastolic blood pressure is considerably higher in both males and females in the Bahama study. Although there are some differences in mean pressure levels in other studies of blood pressure in white Americans, the data summarized by Master et al. are, in general, comparable to that collected by other investigators.

Further comparisons of the Bahama data with that of white persons in the United States and Negro subjects in the Virgin Islands reveal that in most ages and in both sexes, the per cent of systolic blood pressure elevations (150 mm. Hg or more) is higher in most categories in the Bahamas, although there is some overlap with the data on Negroes in the Virgin Islands (Fig. 6). Both studies reveal a considerable difference between blood pressure in Negro persons as compared to data on whites. Although results of systolic blood pressure in Negro inhabitants of the United States are not summarized in this illustration, they roughly parallel the data illustrated for the Bahamas (see Figs. 1 and 3, Comstock).

Table II summarizes the prevalence of "hypertension" as defined by a systolic pressure of 150 mm. Hg or more or a diastolic pressure of 100 mm. Hg or more in a group of Negroes in the United States, the Grand Bahama Island, Nassau and Rolleville, a small community on Exuma, an island in the southern part of the Bahamas. (The adult population of 130 persons in Rolleville is entirely Negro with no white admixture and living conditions are primitive with few modern conveniences. Blood pressure was recorded on all the adult inhabitants.) The percentages for the United States are taken from Comstock,[3] and those from Grand Bahama Island represent a summary of 1,595 persons who were examined as noted under "Material and Methods." Prevalence of "systolic hypertension" in Nassau compares closely with that of Negroes in Georgia, whereas

the per cent of systolic hypertension in Grand Bahama Island is somewhat lower, and in Rolleville, somewhat higher. All these percentages are considerably higher than comparable data in white subjects, both in the United States and elsewhere. The percentage of diastolic hypertension in both sexes is higher in Grand Bahama Island and Rolleville than it is in the United States, and Nassau. It is considerably higher in the male group in Nassau as compared to the Comstock, Georgia, study, although the females are approximately equivalent. These data have not been standarized for age.

There appeared to be a marked variation in the average blood pressure of different community groups on Grand Bahama Island. For example: In Sweeting's Cay the prevalence rate of hypertension, defined as one or more blood pressure readings of 150/100 mm. Hg or more, was 34.1 per cent, for both sexes. In Maclean's Town, a community about 15 miles distant by water, the prevalence rate was 16.7 per cent. These villages were similar in total population, mode of living, dietary habits and occupations but there had been little intermarriage between the two communities.

TABLE II

Per cent Prevalence of Systolic* and Diastolic† "Hypertension" Observed in Negroes by Area and Sex, Not Standardized for Age

Sex	U.S.A.	Grand Bahama	Nassau	Rolleville Exuma‡
		Systolic "Hypertension"		
Males	29.8	27.1	29.3	40
Females	35.0	25.8	33.8	42
		Diastolic "Hypertension"		
Males	4.8	35.4	19.5	37.5
Females	23.0	34.0	24.2	48.8

* 150 mm./Hg or more.
† 100 mm./Hg or more.
‡ Total adult population (130).

EVALUATION OF FACTORS OTHER THAN BLOOD PRESSURE

Examination of the urine of 420 subjects, 130 of whom were from Rolleville, failed to reveal significant abnormalities in over 90 per cent of the group tested. Although microscopic examinations were not performed, the lack of albuminuria was accepted as reasonable evidence against significant renal disease as a contributing factor to the high degree of prevalence of "elevated blood pressure." Glycosuria was even more uncommon than albuminuria. Conditions of the study made it extremely difficult to evaluate renal function more carefully in a large group of subjects.

Blood urea nitrogen determinations in fifty selected ambulatory hypertensive patients with blood pressure of 150/100 mm. Hg or more were within normal limits or low in forty-eight cases. This may, of course, be the result of poor protein intake and not reflect accurately the degree of renal failure present in the hypertensive population. Only nine of these patients had a trace or more of albuminuria.

Electrocardiographic and chest roentgenographic studies were also carried out on these fifty patients with moderately severe to severe hypertension. Twenty of the fifty electrocardiograms were abnormal. Five showed findings consistent with early left ventricular hypertrophy and nine exhibited advanced left ventricular hypertrophy. Six tracings showed non-specific T wave abnormalities but none exhibited any changes that could be interpreted as being due to recent or old myocardial infarction. Cardiac hypertrophy was noted in twenty-three patients on chest roentgenograms.

Obesity was a common occurrence among the subjects evaluated, especially among women over the age of twenty-five. In many instances weight was estimated to be 30 or more pounds over the average. This may be a factor in explaining the higher blood pressures noted in the females studied because of the marked increase in arm girth. Forearm or intra-arterial pressures were not taken in this group.

DIETARY HABITS. SALT INTAKE

Careful dietary studies have not as yet been carried out, but some information regarding the dietary habits of the Bahamians is worth noting. The native diet on the smaller islands consists primarily of peas, grits, rice and fish. Much of the food is fried in salt pork oil, but little or no meat or dairy products are available as sources of protein. Much of the fish is salted and preserved by drying in the sun. On the island of New Providence, fish is more plentiful and meat and other foods are available to many of the natives who work in the hotels and resort clubs.

Studies are presently in progress in an attempt to confirm initial impressions that sug-

gest a high sodium intake on both the smaller islands and in Nassau. It has been confirmed that most well water on the Islands has a significantly high sodium content (100 to 150 mg. sodium per 100 cc. as compared to average U.S.A. water supply of 0.3 to 0.4 mg. sodium per 100 cc.). Twenty-four hour sodium excretion studies on a limited number of subjects suggest that the daily sodium intake of between 15 to 30 gm. is higher in the Bahamas than in the United States, but definite conclusions cannot be drawn from the data available at present. Serum sodium determinations on fifty normotensive and hypertensive persons were within normal limits with no difference being observed between the two groups.

Comments

It is extremely difficult to compare the data of one epidemiologic study of a disease, especially a study of blood pressure, with that of another, because of the differences in sampling technics and methods of recording blood pressure. Other variations of procedure also occur occasionally because of differences in local conditions. The present study was organized in such a manner that at least some of the variables inherent in any large scale field study would be eliminated, although certain obvious biases in the data are present.

Since many of the persons examined were part of the "patient" population in both private and hospital practice, we can assume that the percentage of hypertensive persons, at least in the older age groups, and *especially* in the females who might attend the hospital clinics more frequently than males, would be higher than if more careful sampling technics were employed. It might also be assumed that the reported blood pressure in the males would be lower than expected in the younger age groups since many of these subjects were healthy laborers who had previously been examined. It may be supposed that many male hypertensive subjects who had previously been rejected because of an elevated blood pressure would not be reapplying for work.

The recording of casual blood pressure also introduces a certain error since it is well known that there may be marked variability in pressure levels from day to day and even during the same day in the same person. In a large scale study of this type many of these "recording" errors might tend to cancel out, making the "trends" if not the "absolute values" useful for comparison with other studies. The sampling biases, however, would not be expected to cancel out and would tend to artificially overemphasize the increase of blood pressure with age.

Despite these variations in procedure and sample selection, the Bahama study appears to confirm previous impressions that hypertension (and hypertensive cardiovascular disease) is more common in the Negro than in the white race. There does not appear to be any great difference in blood pressure levels in areas that are primitive, such as Rolleville and villages on Grand Bahama Island, as compared to areas where "civilization" has progressed and the native has been "urbanized." There appears to be little or no difference in blood pressure levels in areas where interracial stress might be an important factor (Nassau), as compared to areas which are not biracial (communities on the Grand Bahama Island and Rolleville). *Intra*-racial stress or particular stresses within a given Negro community cannot, of course, be dismissed as contributing factors to explain the increased prevalence of elevated blood pressure in these groups.

Preliminary data suggest that cardiovascular disease is not uncommon as a complication of elevated blood pressure in the Bahamas. Elevated blood pressure does not appear to occur as a "benign" finding. Electrocardiographic abnormalities apparently occur with about the same frequency as noted in a "hypertensive" population in other areas although graphic evidence of coronary artery disease or myocardial infarction is rare. Congestive heart failure as a complication of hypertension *is* observed in the hospital population in Nassau. Renal failure and "accelerated" forms of hypertension are also seen in hospital patients although the exact percentage of these cases has not been determined. The most frequent complication of hypertension in the Bahamas appears to be cerebral hemorrhage, a finding in common with data in other Negro populations. The leading cause of "cardiovascular" deaths in Nassau and the smaller islands is listed as cerebral hemorrhage.

A high salt intake or familial transmission of hypertension may be of some importance as factors contributing to the high prevalence of hypertension in this population.

Preliminary data, as noted, suggest a salt intake of between 15 and 30 gm. daily. There was little apparent difference in the salt intake, however, of the inhabitants of Sweeting's Cay

and of MacLean's Town, despite a substantial difference in the prevalence of hypertension. Differences in the familial characteristics of these two socially isolated communities would seem to provide a more rational explanation of the varying prevalence of hypertension, while the similar frequency of the disease in Negroes in Georgia, the Virgin Islands and the Bahamas would suggest that a racial susceptibility exists.

A recent report of a similar frequency of high blood pressure in the Negro in the Belgian Congo (Van Dooren, Proceedings World Congress of Cardiology, Brussels 1958) supports the idea of a racial predisposition and minimizes the possibility that an environmental factor alone is responsible for the high prevalence of hypertension in the American Negro. It is possible of course that both factors may be important: That a high salt intake in these regions exacerbates an inborn tendency to hypertension. Until the blood pressure of American Negroes subsisting on different levels of salt intake is known, the possibility cannot be excluded that both dietary and familial factors are involved in the genesis of hypertension in this area.

Summary

1. Data on a blood pressure study of 3,594 Negro subjects in the Bahamas are presented. These data confirm previous observations that the prevalence of elevated blood pressure in this area is high. The percentage of males with a blood pressure of 150/90 mm. Hg or more was 25 per cent; of females, 30 per cent.

2. Comparisons of these data with the blood pressure of white subjects in the United States revealed significantly higher systolic and diastolic blood pressures in both sexes and in all age groups in the Bahamas.

3. Blood pressure levels of three different Negro populations (United States, Virgin Islands and the Bahamas) were compared and found to be similar in most age groups. This suggests that the blood pressure of Negroes is higher regardless of areas studied or level of "civilization." Significant differences in blood pressure were not found between "rural" or "urban" areas in the Bahamas.

4. Complications of elevated blood pressure, especially cerebral hemorrhage, are apparently common in the Bahamas.

5. Although salt intake may be high in the natives of the Bahamas, familial factors may be of more importance in explaining the variability of prevalence in different island groups in this apparently "susceptible" population.

6. Additional genetic and dietary studies are suggested in this group as well as in comparable Negro populations elsewhere in an effort to clarify the apparent "racial" susceptibility to hypertension.

Acknowledgment

We are indebted to Dr. E. H. Murcott, Chief Medical Officer of the Bahamas, and Drs. Lorenz and Esfakas, in Nassau, for their assistance in this phase of the study.

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Observations on Flumethiazide in the Treatment of Essential Hypertension*

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AMONG the many causative factors in the pathogenesis of essential hypertension, sodium has been implicated by numerous investigators, at least as a factor responsible for aggravation of the hypertensive state. Conversely, depletion of body sodium, by means of decreased intake or increased excretion of salt, has become a valuable therapeutic approach.

An effective way of reducing body sodium is by the use of diuretics. The orally administered, active diuretic, chlorothiazide,[1] has proved to be beneficial in the treatment of hypertension.[2–5] The successful use of this compound stimulated the synthesis and study of new analogues, particularly in the hope of finding an agent which would produce less kaliuresis. One new compound, flumethiazide, was found to be an effective saluretic agent in the clinical studies of Fuchs and Bodi et al.[6,7] which led the way to the current study using it in the treatment of hypertension. A preliminary study[8] was encouraging and it was found that the effect was more pronounced when flumethiazide was given in combination with rauwolfia. The objectives of this study were to evaluate the antihypertensive effect of flumethiazide and the potentiating and additive influence of rauwolfia upon this response and vice versa.

METHOD AND MATERIALS

Thirty-four ambulatory patients with blood pressures greater than 150/90 mm. Hg were randomly placed into two different groups. After an initial diagnostic evaluation, they were given a placebo daily for at least three weeks. They returned to the clinic at weekly intervals and their blood pressure, physical signs and symptoms were recorded. After the control period flumethiazide† was given to the first group (A) in a dose of 500 mg. twice a day for two months and rauwolfia‡ was given to the second group (B) in a dose of 100 mg. twice a day for the first week, and 50 mg. twice a day for the next seven weeks. At the end of this two-month period, eleven patients from each of the previous groups received a combined therapeutic program when rauwolfia was added to flumethiazide in the first group and flumethiazide was added to rauwolfia in the second. The combined therapy was continued for another two months in this group (C). Flumethiazide was administered as previously in a dose of 500 mg. twice a day and rauwolfia in a dose of 50 mg. twice a day for the remainder of the study. Both drugs were given orally. Electrolyte determinations, complete blood counts and urinalyses were performed during the control period, after one week of therapy and at the end of each period of study. Throughout the period of treatment the patients were advised to remain on the same diet.

RESULTS

GROUP A: FLUMETHIAZIDE GIVEN ALONE

The effects on blood pressure are tabulated in Table I. Of the seventeen patients who took flumethiazide for two months, seven (41 per cent) obtained a drop in mean blood pressure of more than 20 mm. Hg in the supine position and two of them (12 per cent) became normotensive. It is interesting to note that when the blood pressure was taken in the upright position nine patients showed a significant response, which represents 53 per cent of the patients treated. Eight became normotensive (47 per cent).

The side and beneficial effects have been listed in Tables II and III, respectively. No serious reactions were noted when flumethi-

† Supplied as ademol by E. R. Squibb and Sons, New York, New York.

‡ Supplied as Raudixin® by E. R. Squibb and Sons, New York, New York.

* From the Hypertension Unit, Department of Internal Medicine, the Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania.

TABLE I

Blood Pressure Response to Flumethiazide and Rauwolfia When Given Alone and in Combination (Expressed in Per Cent of Number of Patients Treated)

Drug	No. of Patients	Supine			Upright		
		Normotensive†	Mean Blood Pressure Reduced >20 mm. Hg or Normotensive	Unresponsive	Normotensive	Mean Blood Pressure Reduced >20 mm. Hg or Normotensive	Unresponsive
Flumethiazide alone (group A)	17	12	41	59	47	53	47
Rauwolfia alone (group B)	17	6	24	76	24	29	71
Rauwolfia plus flumethiazide (group C)*	22	36	50	50	59	68	32

* Group C: Consists of eleven patients who received flumethiazide then rauwolfia and eleven patients who received rauwolfia and then flumethiazide.

† Blood pressure reduced to 150/90 mm. Hg or less.

azide alone was administered. Some dryness of the mouth, increase in appetite, general malaise and dreams were the most frequent complaints but were seen in only a few patients. When flumethiazide was given together with rauwolfia approximately 18 per cent of the patients complained of nasal congestion and dryness of the mouth. Nine per cent experienced slight emotional depression which disappeared when the medication was discontinued. The increase in appetite was not significantly greater than when flumethiazide was given alone and the significance of this observation is questionable since it was not associated with a gain in weight.

Flumethiazide alone improved headache in only two of seven patients, reduced dyspnea in two of three patients, improved chest pain in one of two patients and improved orthostatic weakness in three of six patients.

GROUP B: RAUWOLFIA GIVEN ALONE

The effects on blood pressure are tabulated in Table I. Among the seventeen patients who took rauwolfia alone for two months, four patients experienced a reduction in mean blood pressure of 20 mm. Hg or more in the supine position and one became normotensive. When the blood pressure was taken in the upright position, five patients had a significant response and four of them became normotensive. This response is somewhat less than that which we have observed previously in patients who have taken rauwolfia.[9]

The side and beneficial effects have been listed in Tables II and III, respectively. When rauwolfia was given alone the main side effect was an increase in appetite which occurred in seven patients (41 per cent). Next in frequency were nasal congestion, anxiety and dizziness which were noticed in four patients (24 per cent). Dreams were experienced by 18 per cent of the patients and one patient had a mild depressive reaction.

Rauwolfia alone improved headache in three of six patients, reduced chest pain in one patient of three, improved nausea and anxiety in one patient of two. Muscle pain disappeared completely in two patients who had this complaint previously. Dyspnea improved in one patient of five.

TABLE II

Side Effects Expressed in Per Cent of Patients Treated

Side Effect	Flumethiazide Alone (Group A)	Rauwolfia (Group B)	Rauwolfia plus Flumethiazide (Group C)
Headache	6	...	...
Dry mouth	12	12	18
Nasal congestion	6	24	18
Edema	...	12	...
Increased appetite	12	41	14
Nausea	6	...	9
Constipation	6	6	9
Anxiety and malaise	12	24	5
Dizziness	6	24	5
Depression	...	6	9
Dreams	6	18	5

TABLE III

Beneficial Effects Expressed in Per Cent of Total Number of Patients with Symptoms Who Were Improved

Symptom	Flumethiazide Alone (Group A)		Rauwolfia Alone (Group B)		Rauwolfia plus Flumethiazide (Group C)	
	No. of Patients Who Complained Before Therapy	Per Cent of Patients Improved	No. of Patients Who Complained Before Therapy	Per Cent of Patients Improved	No. of Patients Who Complained Before Therapy	Per Cent of Patients Improved
Headache	7	29	6	50	11	55
Chest pain	2	50	3	33	2	100
Nausea	..	..	2	50	1	100
Constipation	4	25	..	..	4	50
Anxiety	3	33	2	50	8	50
Orthostatic weakness	6	50	..	..	4	50
Muscle and joint pains	8	25	2	100	4	25
Dyspnea	3	66	5	20	2	100
Edema	2	100	..	..	4	100

GROUP C: COMBINATION OF RAUWOLFIA AND FLUMETHIAZIDE

Among the twenty-two patients who received combined therapy with rauwolfia and flumethiazide, 50 per cent obtained a significant reduction in blood pressure in the supine position and 68 per cent in the upright position. Thirty-six per cent became normotensive in the supine and 59 per cent in the upright position. It was of interest to note that the blood pressure response was greater when the rauwolfia was added after the flumethiazide had been given for the previous two months. Of the eleven patients who received flumethiazide first, 73 per cent obtained a significant reduction in blood pressure in the upright position as compared to 64 per cent when the rauwolfia was given for two months and then flumethiazide was added. The contrast was greater when supine blood pressures were recorded in that 73 per cent responded to combined therapy when flumethiazide was given first but only 24 per cent responded when the rauwolfia was given first.

Side effects were as expected and consisted primarily of nasal congestion, dry mouth and some of the other minor responses as recorded in Table II.

Symptomatic improvement was associated with a significant reduction in the incidence and severity of headache and precordial pain. Dyspnea and edema were reduced in all patients who had these complaints prior to therapy.

PLASMA ELECTROLYTES AND CHEMICAL STUDIES

In none of the groups were there marked changes in the plasma electrolytes and blood urea nitrogen (Table IV). In group A, the mean value of blood urea nitrogen ranged between 11 and 13 mg. per cent and in group B between 14 and 18 mg. per cent in the different periods, with a range of 5 to 18 mg. per cent in group A and 8 to 50 mg. per cent in group B. The control value of the patient with the blood urea nitrogen of 50 mg. per cent was 35 mg. per cent and the increase appeared when the patient was receiving the combined therapy.

The average plasma sodium dropped slightly in group A, from a control value of 146 to 141 mEq./L. after two months of treatment with flumethiazide and did not change (142 mEq./L.) on combined therapy. The range was 136 to 152 mEq./L. In group B, the plasma sodium increased slightly after two months on combined therapy from 142 to 147 mEq./L. with a range of 130 to 152 mEq./L.

The mean plasma potassium in group A dropped slightly from 4.7 to 4.4 mEq./L. in the first two months and increased to 4.5 mEq./L. in the next two months. The plasma potassium dropped to 3.2 mEq./L. in only one patient, but stayed above 4.0 mEq./L. in the remainder of the patients. In group B, the plasma potassium dropped slightly after two months of combined therapy from 4.7 to 4.5 mEq./L. and in the same period the plasma potassium fell

TABLE IV

Effect of Flumethiazide and Rauwolfia Given Alone and in Combination on Plasma Electrolytes and Blood Urea Nitrogen

	Blood Urea Nitrogen (mg. per cent)			Plasma Na (mEq./L.)			Plasma K (mEq./L.)		
	Control	D_1	D_2	Control	D_1	D_2	Control	D_1	D_2
Patients in Group A									
Mean	11	12	13	146	141	142	4.7	4.4	4.5
Range	5–16	7–18	10–15	136–152	136–148	136–150	4.0–6.0	3.2–6.0	3.8–5.4
Patients in Group B									
Mean	14	11	18	142	142	147	4.8	4.7	4.5
Range	9–35	8–36	8–50	130–149	135–151	136–152	4.1–5.6	3.7–6.1	3.6–5.7

NOTE: In group A, D_1 = flumethiazide; D_2 = flumethiazide plus rauwolfia (eleven patients, i.e., first half of patients in group C). In group B, D_1 = rauwolfia; D_2 = rauwolfia plus flumethiazide (eleven patients, i.e., second half of patients in group C).

to 3.6 mEq./L. in only one patient. The range was from 3.6 to 6.1 mEq./L.

COMMENTS

Blood Pressure: In previous studies Fuchs and Bodi et al.[6,7] observed that flumethiazide has properties similar to chlorothiazide. In patients who were not edematous, there was no difference in natriuretic potency between chlorothiazide and flumethiazide.

In group A, we used 1 gm. of flumethiazide daily (500 mg. given twice a day) and the blood pressure response rate (41 per cent), when the blood pressure was taken in the supine position, compared favorably with the results obtained with chlorothiazide in patients with hypertension; only 12 per cent became normotensive. The number responding was greater (53 per cent) when the upright mean blood pressure was taken for comparison and 47 per cent became normotensive. On combined therapy (flumethiazide and rauwolfia) the results were better (68 per cent), indicating an additive effect. An orthostatic effect was noted when the blood pressure was taken in the upright position.

In group B, when rauwolfia was given alone in a dose of 50 mg. twice a day, the response rate of about 30 per cent when the upright blood pressure was recorded is somewhat lower than in other series.[9] The combined therapy showed a better response. The difference in response between supine and upright positions should be emphasized, especially since the pronounced orthostatic effect seems to be caused by the flumethiazide. This orthostatic effect has not been reported previously in the literature, but was noticed previously in our study with chlorothiazide.[4]

Gain in Weight: When taking rauwolfia alone, fourteen patients showed a gain of weight in the range of 1 to 6 pounds with an average of 2 pounds. When flumethiazide was added, the increase in body weight continued and the average gain was 1 to 3 pounds.

In contrast to the observations of Fuchs et al.[6] that after five weeks of treatment with flumethiazide in patients with congestive heart failure there was an average decrease of 1.2 pounds in body weight, most of our patients with hypertension (fifteen patients) without signs and symptoms of congestive heart failure showed an insignificant change in body weight (average gain 0.6 pounds) after receiving flumethiazide alone for two months. The body weight increased 5 pounds after rauwolfia and flumethiazide were given in combination for the next two months.

Correlation of Blood Pressure and Weight Changes: It seems that in 40 per cent of the patients the changes in blood pressure closely paralleled the changes in body weight following the ad-

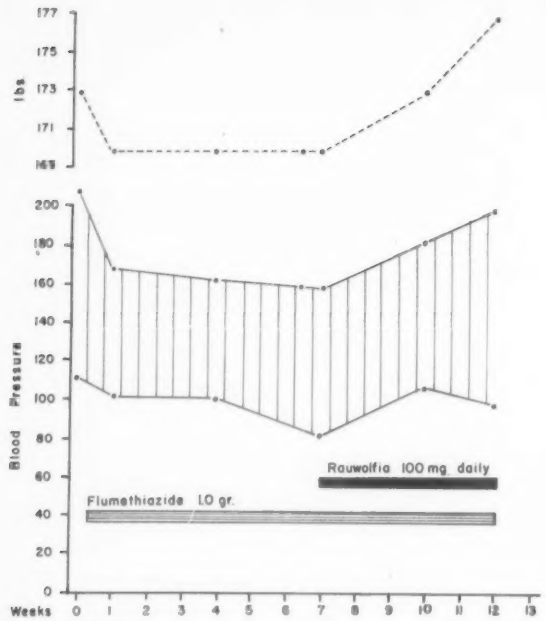

FIG. 1. *Blood Pressure Changes Related to Body Weight Changes.* The patient received flumethiazide for eight weeks followed by the administration of a combination of flumethiazide and rauwolfia. Following the initial diuresis and weight loss the blood pressure decreased. When rauwolfia was added there was actually an increase in blood pressure as the weight increased. This was an unusual response in that the majority of the patients who responded to flumethiazide initially showed an additional reduction in blood pressure when rauwolfia was added to the regimen.

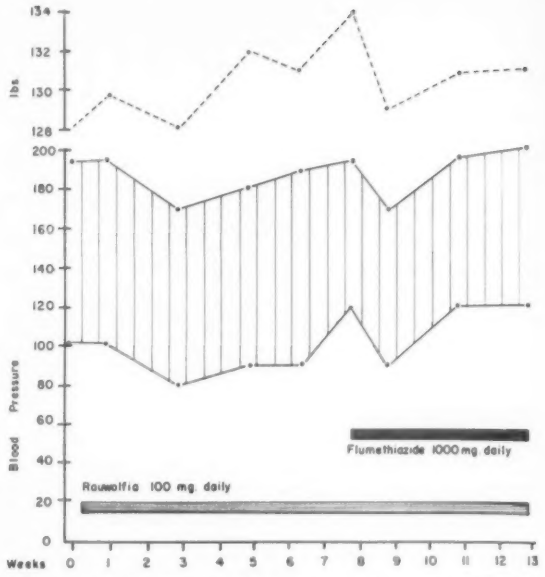

FIG. 2. *Blood Pressure Changes Related to Body Weight Changes.* Blood pressure response to flumethiazide in a patient who was receiving rauwolfia also. When flumethiazide was added there was a sharp reduction in body weight associated with a decrease in blood pressure. After three weeks the patient gained weight again and this was associated with an increase in blood pressure to the preflumethiazide level.

ministration of flumethiazide (Figs. 1, 2 and 3). For example, in patient L. B. (Fig. 1) the blood pressure decreased from 210/115 to 170/108 mm. Hg after she received flumethiazide for one week and then to 160/84 mm. Hg at the end of the eight weeks. At the same time her body weight was reduced from 173 to 169 pounds. At the end of the eight weeks, rauwolfia was added to the flumethiazide but the blood pressure rose to 184/110 mm. Hg after three weeks and to 200/100 mm. Hg after five weeks. At the same time her body weight increased from 169 to 177 pounds. The cause for the increase in body weight after rauwolfia was added is not apparent. It may be that the rauwolfia caused a retention of salt and water which was associated with an increase in blood pressure. This response was observed occasionally but usually the administration of rauwolfia was associated with an additional reduction in blood pressure.

In the second patient, L. D. (Fig. 2), the blood pressure dropped from 190/100 to 170/80 mm. Hg after she received rauwolfia for three weeks and then started to increase slightly and at the end of the eight weeks was 195/120 mm. Hg. At the same time the fol-

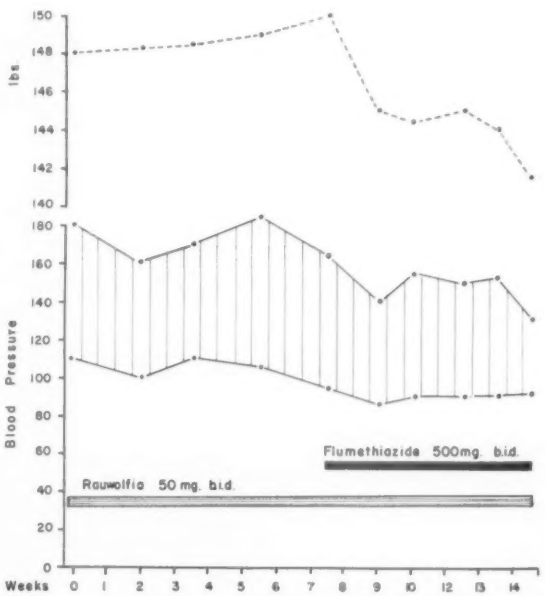

FIG. 3. *Blood pressure response to flumethiazide,* showing a parallel reduction in weight and blood pressure.

lowing changes were observed in her body weight: one week after rauwolfia therapy, the body weight rose from 128 to 130 pounds; by the end of the third week (the time of the maximal effect of rauwolfia) it dropped to 128 pounds and then increased from 128 to 134 pounds after eight weeks. When flumethiazide was added the blood pressure fell from 194/120 to 170/90 mm. Hg after one week of therapy, then after two weeks rose to 195/120 mm. Hg and after six weeks was 196/121 mm. Hg. At the same time her body weight was reduced from 134 to 129 pounds one week after flumethiazide was started but it increased to 131 pounds at the end of the third week and was still 131 pounds after six weeks. This loss of blood pressure response suggests that tolerance to the drug has developed. A parallel reduction in body weight and blood pressure was also observed in the patient whose response is shown in Figure 3 but the response was maintained in this patient throughout the period of observation.

In some of our patients no apparent relationship between blood pressure and body weight was observed (Fig. 4). These results confirm the previous observations of Rochelle et al.[10] who found that 41 per cent of their patients showed a decrease in the blood pressure associated with either a steady weight or a slight reduction in weight while receiving chlorothiazide. Collateral antihypertensive drug therapy may play "a significant role" in this response.

Mechanism of Hypotensive Effect: We may presume that flumethiazide, which possesses the same pharmacologic properties as chlorothiazide, is effective by the same mechanism. Although the mode of action of chlorothiazide in patients with hypertension is still unsettled, it seems most likely that the drug produces its effect by a reduction in plasma volume and an increase in the excretion rate of sodium, resulting in a relative depletion of tissue sodium at the neuro-effector site. But as Freis[11] has pointed out, "once the labile pool of extracellular fluid has been skimmed off, chlorothiazide seems to become relatively ineffective in removing further sodium." For example, in patient L. B. (Fig. 1) we may assume that one week after the start of the therapy with flumethiazide the reduction of the extracellular fluid was maximal and this was reflected in the maximal drop of the blood pressure at that time. Then, there was no further loss of weight

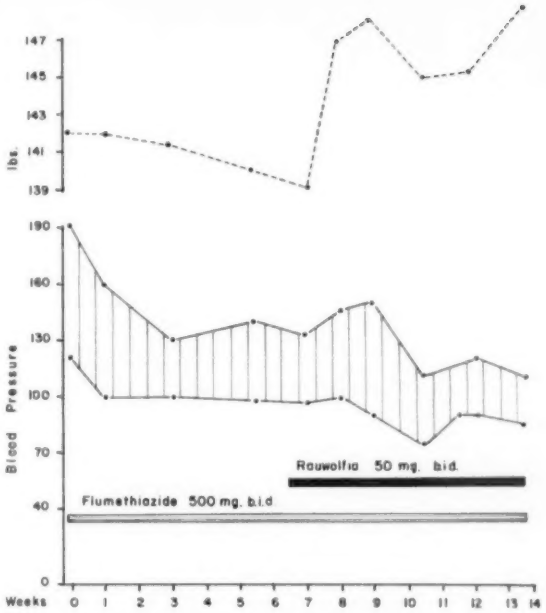

FIG. 4. *Blood pressure response to flumethiazide*, showing no correlation between weight change and blood pressure.

and the blood pressure was quite stable. The addition of rauwolfia increased the body weight and a rise in blood pressure followed. This pattern was noticed in three of our patients receiving this combination, but, in about half the blood pressure fell, although the body weight increased when rauwolfia was added to the flumethiazide. It may be that in some patients the increase in body weight is due to sodium and water retention associated with rauwolfia administration while in other instances it is due to increased intake of food. As noted previously, some patients show no relationship between body weight and blood pressure response. These results were puzzling and we were inclined to favor the suggestion of Alexandrow et al.[12] that the reduction in blood pressure is caused primarily by a decrease in the peripheral resistance and should be, therefore, independent of changes in body weight.

In a recent publication Dustan et al.[13] suggested that chlorothiazide decreases plasma volume and this tends to decrease the arterial pressure. The "homeostasis" of hypertension then results in increased vasomotor tone, tending to sustain pressure. At this point the administration of an agent which diminishes vasomotor tone reduces arterial pressure more efficiently than it would in the absence of increased vasomotor tone. A consequence of

this assumption will be that there should be a greater beneficial effect by beginning the treatment with a diuretic. The current study confirms this point. The patients in group A, who were started on flumethiazide and then rauwolfia was added, had a better blood pressure response (73 per cent) than the patients in group B, who were started on rauwolfia and then flumethiazide was added, resulting in a significant reduction of pressure in only 64 per cent of the patients.

Summary

1. Flumethiazide (ademol) given in a dose of 500 mg. twice a day for two months has proved to be an effective antihypertensive agent in 41 per cent of patients with mild hypertension as measured by blood pressures recorded in the supine position. A slight orthostatic hypotensive effect was noted in that 53 per cent responded as measured by blood pressures recorded in the upright position. Only 12 per cent of the patients became normotensive as measured by blood pressures recorded in the supine position. Minimal side effects were observed.

2. A significant additive effect on blood pressure was noted when rauwolfia (whole root) and flumethiazide (ademol) were given in combination. The results were better when flumethiazide, rather than rauwolfia, was given prior to the combined therapy. Combined therapy using 500 mg. of flumethiazide given twice a day and 50 mg. of rauwolfia given twice a day for two months resulted in a significant reduction in blood pressure in 73 per cent of the patients when flumethiazide was given first and in 64 per cent when rauwolfia was given first.

3. An orthostatic hypotensive effect was noticed when flumethiazide was given alone or in combination.

4. A relationship between a decrease or increase in body weight and a decrease or increase in the blood pressure was noted.

5. Causes for the slightly different responses in groups A and B are discussed.

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A Comparison of Hydrochlorothiazide and Chlorothiazide in the Treatment of Hypertension*

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THE CONCEPT that diuretic agents would produce the same effect as restriction of dietary salt in lowering blood pressure prompted their use in antihypertensive programs. With the availability of chlorothiazide, an oral diuretic with potency comparable to the parenteral mercurial agents, it became possible to employ continuous diuretic therapy in conjunction with antihypertensive agents.

The mechanism of action of chlorothiazide has been studied extensively. While it has been suggested that the drug has a primary, independent antihypertensive effect, the evidence suggests that reduction of blood pressure is secondary to loss of salt. Whether salt is removed only from the extracellular fluid or, as more recently suggested, from salt-laden arterial walls, muscles or elsewhere, is not yet certain. It is of interest to learn if an additional hypotensive effect would occur if still greater natriuresis could be produced.

Attempts to increase excretion of salt by raising the dosage of chlorothiazide have not been successful. No appreciable increase in sodium excretion has been demonstrated with doses above 2,000 mg. daily. At this high dosage level potassium and chloride excretions are significantly high, so that hypopotassemia and hypochloremic alkalosis may readily develop. These limitations have prompted the search for more potent diuretic agents.

By hydrogenating the one double bond in the heterocyclic ring of chlorothiazide a derivative was produced (hydrochlorothiazide) that, when given intravenously in dogs, had more than ten times the natriuretic effect of the parent compound.

Prior to considering the effect of hydrochlorothiazide in the treatment of hypertension the potency of this compound as a diuretic was evaluated. While comparative studies of this type are admittedly inexact, it is our impression that hydrochlorothiazide (150 mg.) will produce a quantitatively greater excretion of both sodium and chloride, with less danger of hypopotassemia, than chlorothiazide (2,000 mg.). Thus hydrochlorothiazide produced 12 per cent greater excretion of sodium, 28 per cent greater excretion of chloride and 2 per cent less potassium excretion than did chlorothiazide at these dosage levels.[1] Dosage of hydrochlorothiazide above 200 mg. did not produce significant additional loss of salt, while excretion of potassium increased. These two compounds have been compared in the treatment of hypertension to determine whether or not additional excretion of salt will produce a further hypotensive effect.

MATERIAL

Seventy-two patients with essential hypertension were the subjects for this study. Most had been followed up for at least eighteen months prior to this study. Their response to antihypertensive therapy and baseline blood pressures were well known. The effect of hydrochlorothiazide was studied in two groups of subjects. In sixty patients, all of whom were receiving chlorothiazide as well as various antihypertensive medications, hydrochlorothiazide was substituted for chlorothiazide while the remaining medications were unchanged. Average blood pressures over twelve-week periods before and after the

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Hydrochlorothiazide (Esidrix®) used in this study was generously supplied by Dr. Edgar Jack, Ciba Pharmaceutical Products, Inc., Summit, New Jersey.
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TABLE I
Hydrochlorothiazide Substituted for Chlorothiazide

Original Antihypertensive Regimen	No. of Patients	Blood Pressure Response after Hydrochlorothiazide Replaced Chlorothiazide	
		Improved with Hydrochlorothiazide*	No Change with Hydrochlorothiazide
Reserpine and chlorothiazide	9	2	7
Reserpine and veratrum and chlorothiazide	9	3	6
Reserpine and hydralazine and chlorothiazide	14	4	10
Hydralazine (over 300 mg.) and chlorothiazide	11	6	5
Ganglionic blocking agent and chlorothiazide	3	3	0
Ganglionic blocking agent and chlorothiazide	6	4	2
Ganglionic blocking agent and reserpine and chlorothiazide	8	5	3
Total	60	27	33

* Reduction in blood pressure (systolic + diastolic)/2 of 10 per cent or more from previous levels.

administration of hydrochlorothiazide were compared. All patients were ambulatory. The dose ranged between 50 and 200 mg. daily, although in most patients the dosage was 50 mg. twice daily.

The second group included twelve subjects with essential hypertension (none in congestive heart failure) who had never (or not recently) recieved any antihypertensive or diuretic agents. These patients received only hydrochlorothiazide in amounts of 100 to 150 mg. daily during an average period of ten weeks. No other medications were given. All patients were ambulatory and pursued their regular occupations. No attempt was made to control the intake of dietary salt, nor were weight reduction programs instituted among the obese patients during this period of observation.

Results

Hydrochlorothiazide Combined with Other Drugs: The effects of replacing chlorothiazide with hydrochlorothiazide in established antihypertensive regimens are shown in Table I.

We have arbitrarily considered any reduction representing 10 per cent or more of previous blood pressure (systolic + diastolic)/2 to be significant. On this basis, twenty-seven of sixty subjects (45 per cent) benefited from the more potent diuretic.

The drug appeared more effective than chlorothiazide when used in combination with the ganglionic blocking agents. Of sixteen patients receiving blocking agents (alone, or with reserpine, or reserpine and hydralazine), eleven of the group (68 per cent) showed additional reduction in blood pressure after receiving hydrochlorothiazide. Of significance is that in four patients previously regulated with blocking agent plus reserpine and chlorothiazide therapy postural hypotensive episodes developed within seventy-two hours after hydrochlorothiazide replaced chlorothiazide in the regimen.

Hydrochlorothiazide also seemed to enhance the effectiveness of hydralazine. This was most apparent in patients receiving more than 300 mg. daily of this agent. Six of eleven subjects showed additional significant lowering of blood pressure. The newer diuretic appeared to offer no clear advantage over chlorothiazide when used with reserpine or with veratrum. However, two subjects who previously required reserpine and chlorothiazide and one patient who originally received reserpine, veratrum and chlorothiazide were controlled adequately with hydrochlorothiazide (150 mg.) daily only. This response could not be duplicated with chlorothiazide alone.

Twenty-eight of the sixty patients lost between 2 and 4 pounds during the period of observation. In the remaining patients weights were unchanged. No correlation was apparent between weight loss and reduction of blood pressure.

Hydrochlorothiazide Alone: The results of the use of hydrochlorothiazide alone among twelve previously untreated patients with essential hypertension are shown in Table II. At the end of a two-week period, eleven patients showed decreases in blood pressure (systolic plus diastolic divided by 2). The reductions ranged from 3 to 21 per cent (average 10.9 per cent) with eight subjects showing decreases of 10 per cent or more. After four weeks the average

TABLE II
Hydrochlorothiazide in Previously Untreated Patients

Case No. and Age (yr.)	Average Blood Pressure (Untreated)		Percentage Change in Blood Pressure* after Hydrochlorothiazide			Weight (lb.)	
	Systolic	Diastolic	2 Weeks	4 Weeks	10 Weeks	Original	After 10 Weeks
1,44	207	123	−10	−6	−4	183	180
2,57	212	122	−18	−17	−15	204	198
3,66	203	114	−16	−11	−5	168	166
4,55	179	103	−11	−7	−3	157	156
5,29	188	109	−6	−8	−4	152	153
6,70	223	128	−12	−8	−4	166	162
7,38	191	111	±0	−2	−2	201	197
8,61	219	122	−21	−17	−13	183	178
9,59	201	114	−13	−11	−11	139	139
10,70	190	110	−9	−3	±10	141	138
11,47	214	125	−12	−8	−3	171	170
12,52	199	117	−3	±0	+2	166	163
Average			−10.9	−8.2	−5.2	169.2	166.8

*(Systolic + diastolic)/2.

reduction was 8.2 per cent but only four patients continued to exhibit reductions greater than 10 per cent. At the end of an average period of ten weeks the decrease in blood pressure averaged 5.2 per cent. Three patients had 10 per cent (or more) reductions of their control blood pressures.

Ten of the twelve patients exhibited weight loss after ten weeks, ranging from 1 to 6 pounds.

Side Effects: Generalized urticaria developed in two patients while they were receiving hydrochlorothiazide. Neither of these patients had known sensitivity to sulfonamide nor did they experience this reaction while receiving chlorothiazide. The urticarial reactions subsided promptly after discontinuation of hydrochlorothiazide and were reproduced on each occasion when hydrochlorothiazide was given. Although both patients were receiving other medications at the time, it was thought that these reactions represented a sensitivity to hydrochlorothiazide. No other side effects of consequence were observed.

Comments

That hydrochlorothiazide is a more potent diuretic than chlorothiazide (on the basis of weight) appears confirmed.[2–4] This fact is of limited significance unless greater excretion of sodium and chloride can be produced by the newer compound. It has been our experience that hydrochlorothiazide (in dosage of 150 mg.) can produce greater natriuresis and chloruresis than chlorothiazide (2,000 mg.). If these findings are valid (a critical view is necessary because of the nature of such comparisons) it would appear that the additional loss of salt achieved with hydrochlorothiazide may be of significance in the further reduction of blood pressure. In this small group, twenty-seven of sixty patients were improved after hydrochlorothiazide replaced chlorothiazide in established antihypertensive regimens.

These data indicate that the hypotensive effect of hydrochlorothiazide is related to changes in salt balance. It is noted that eight of twelve previously untreated patients showed a significant hypotensive effect (greater than 10 per cent reduction of control blood pressure) after two weeks. However, at the end of ten weeks only three of these eight persons could be maintained at the lowered levels. The average decrease in blood pressure after two weeks (for the entire group) was 10.9 per cent but after ten weeks of continuous therapy the average reduction of pressure was only 5.2 per cent. There was an obvious loss of effectiveness during this period. Data described by Fries et al.[5] on chlorothiazide make this diminishing effect more apparent. It appears that these diuretic agents produce a "washing out" of salt at the onset of treatment which is associated with an immediate hypotensive effect, but subsequently new salt levels are established so that the original effec-

tiveness is diminished. Some hypertensive patients can be controlled completely with this potent diuretic agent but most patients eventually require other antihypertensive agents as well for maximum effect.

Summary

A comparison of hydrochlorothiazide and chlorothiazide in the treatment of hypertension has been attempted in seventy-two patients.

In sixty patients with essential hypertension, who were receiving chlorothiazide as well as various antihypertensive agents, hydrochlorothiazide was substituted for chlorothiazide. The remaining program was unchanged. Twenty-seven of the sixty subjects showed reductions in blood pressure of 10 per cent or more of the former levels. This enhanced effect was most apparent among those receiving ganglionic blocking agents or large amounts of hydralazine.

Twelve ambulatory subjects with untreated hypertension were given only hydrochlorothiazide for an average period of ten weeks. There was a significant response in eight patients after two weeks but at the end of ten weeks only three patients could be maintained at the lowered levels.

The effectiveness of hydrochlorothiazide is believed related to its superior ability to quantitatively increase the excretion of salt.

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Clinical Evaluation of Trimethidinium Methosulfate

A New Ganglioplegic Agent*

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ALTHOUGH a wide variety of potent compounds has been developed in recent years for the treatment of essential hypertension, none is effective universally and all have limitations of varying degrees. For this reason the quest for better hypotensive drugs continues and has led to the development of a new ganglionic blocking compound N-(gamma-Trimethylammoniumpropyl) - N - Methyl - camphidinium-di-methyl-sulfate, trimethidinium methosulfate (Wy-1395), an asymmetric bisquaternary amine in which antihypertensive properties have been demonstrated.

Experimental data have shown that trimethidinium methosulfate might be a more satisfactory ganglionic blocking drug since it seemed to combine low toxicity, reasonable duration of action, high potency due to central and ganglioplegic effects and less depressing action on gastrointestinal motility.[1–6]

MATERIAL AND METHODS

Thirty-seven patients were treated with trimethidinium methosulfate.† However, results in only twenty are reported because they were seen at almost weekly intervals while follow-up in the others was inadequate. All serious complications found in the entire group of thirty-seven are reported. Severity of the hypertensive disease was classified by Goodyer's criteria.[7] Of the twenty patients, the hypertension in two was classified as severe, in fifteen as moderate and in three as mild. Most of the patients initially received pentapyrrolidinium which was gradually replaced by trimethidinium methosulfate while other medications were unchanged or discontinued. Except in two cases subsequently discussed, no new hypotensive medications were introduced during the study.

Of the twenty patients treated nineteen were females and one was male. Their ages varied from forty-one to seventy-two years with a mean of 54.2. There were fifteen Negro and five white patients. All had cases of essential hypertension, the duration of which varied from two to twenty-four years with an average of 10.8 years. Of the significant associated diseases, angina was seen in one patient, diabetes mellitus in three, obesity in three and residual hemiparesis as a result of a previous cerebral vascular accident in one. Three patients showed anxiety depression.

Each patient gave a detailed history and received a physical examination and laboratory evaluation.

Control Blood Pressure: Control blood pressure was determined by averaging the blood pressures taken weekly, as described subsequently, for a minimum of four weeks without treatment. During each visit to the clinic four blood pressure determinations were recorded, the first with the patient in the sitting position, the second immediately afterwards in the supine position, the third ten minutes later while remaining in the supine position and the fourth reading followed at once with the patient in the erect position. The blood pressure readings used in compiling the results of this study are the third and fourth.

Dosage: Trimethidinium methosulfate was given initially in two doses of 20 mg. each at twelve-hour intervals before the morning and evening meals. Each dose was increased by 5 to 15 mg. weekly until the level of the erect blood pressure was reduced to 140/95 mm. Hg or untoward side effects limited further increase of the dose. When the total daily dose of trimethidinium methosulfate exceeded 200 mg., the drug was given in three divided doses, before breakfast, at 3:00 P.M. and at bedtime.

Grading of Side Effects: Side effects were graded from 1 to 3 plus. In general, 1 plus represents mild

† Ostensin®, trimethidinium methosulfate, available from Wyeth Laboratories, Philadelphia, Pennsylvania.

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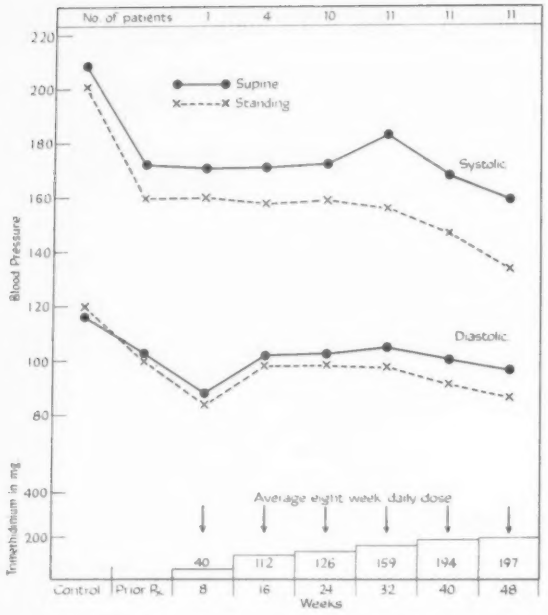

FIG. 1. Blood pressure response to trimethidinium in excellent response group. In this and the following illustrations each dot or X represents the average blood pressure for that eight-week period. Each column represents the average dose of trimethidinium for the corresponding eight-week period.

reactions which do not interfere with ordinary activities, 2 plus represents moderate side effects which occasionally interfere with normal activities and 3 plus represents severe side effects which result in inability to perform normal activities. Constipation was recorded as 1 plus if the patient used a laxative more than once each week, but did not require more than one enema per week; it was 2 plus if two enemas were required and 3 plus if three or more enemas were required.

Prevention of Constipation: In order to attain regular absorption of the drug, it was our aim that each patient have a bowel movement each morning. To achieve this result various simple laxatives were tried and if effective, were continued; however, Prostigmin® was the most dependable medication. The best results were obtained by oral administration of 15 mg. at half-hour intervals until three doses were taken or defecation occurred. If this did not take place patients were instructed to take an enema.

Total daily trimethidinium methosulfate dosages of 400 mg. or more almost invariably necessitated the administration of two or more Prostigmin tablets daily. The morning dose of trimethidinium methosulfate was routinely withheld until a bowel movement was obtained.

Of the twenty patients described, fifteen had been receiving pentapyrrolidinium, one mecamylamine and four no previous ganglioplegic therapy. The degree of response to pentapyrrolidinium was calculated from the determinations of average blood pressure taken during the last six months of this therapy.

Grading of Blood Pressure Response: An excellent response was said to have been achieved when the standing diastolic pressure was consistently less than 140/95 mm. Hg, and side effects were minimal or absent. A moderate response was said to have been attained when the standing diastolic pressure was consistently between 95 and 105 mm. Hg, and side effects were no more than moderate. A fair response was said to be present when the standing diastolic pressure was above 105 mm. Hg but showed a significant reduction (15 mm. Hg or greater), or when the diastolic pressure was inconsistently reduced to levels below 105 mm. Hg, and when side effects were no more than moderate. A poor response was said to have occurred when the standing diastolic pressure was not significantly reduced, when the diastolic pressure was inconsistently reduced to levels above 105 mm. Hg or when side effects were severe.

Fatal Cases: Six deaths occurred in patients who had been or were taking the drug. In four cases, trimethidinium methosulfate was administered for brief periods of time but had been withdrawn at least several weeks prior to death. In one patient, subsequently found to have diverticulitis of the colon with partial obstruction, ileus was precipitated by a dose of 60 mg. per day and the drug was withdrawn. The patient recovered from this but died some weeks later of hemorrhage from a gastric ulcer. Another patient withdrew from the clinic after a brief trial with trimethidinium methosulfate. She subsequently proved to be intolerant to all of the commonly used ganglionic blocking agents and died of a cerebral vascular accident and congestive heart failure. The third patient died of renal failure three months after a brief trial of trimethidinium methosulfate was discontinued; administration of the drug was stopped due to an episode of hypotension and evidence of increasing uremia. A fourth patient died of influenzal pneumonia while taking the medication but complete data were not available for reporting. The fifth patient died of a cerebral vascular accident while taking the drug but is also excluded from the report because of inadequate information. The sixth patient died of a cerebral hemorrhage after failing to come to the clinic or to take trimethidinium methosulfate for three months. Adequate data are not available to include this case in the reported series.

RESULTS

Effect on Blood Pressure: Eleven patients had an excellent response, four had a moderate response, two a fair response and three a poor response (Figs. 1 to 3). The duration of trimethidinium methosulfate administration varied from twenty-four to forty-eight weeks with an average of thirty-five weeks. The average daily dose of trimethidinium methosulfate was 334

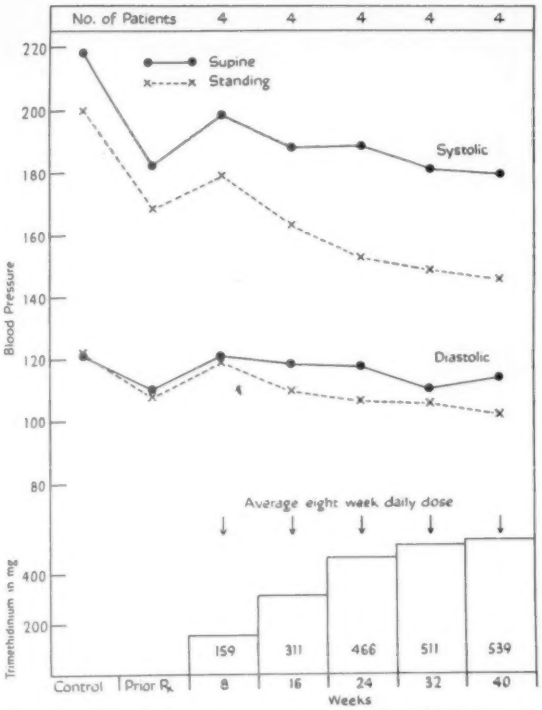

FIG. 2. Blood pressure response to trimethidinium in moderate response group.

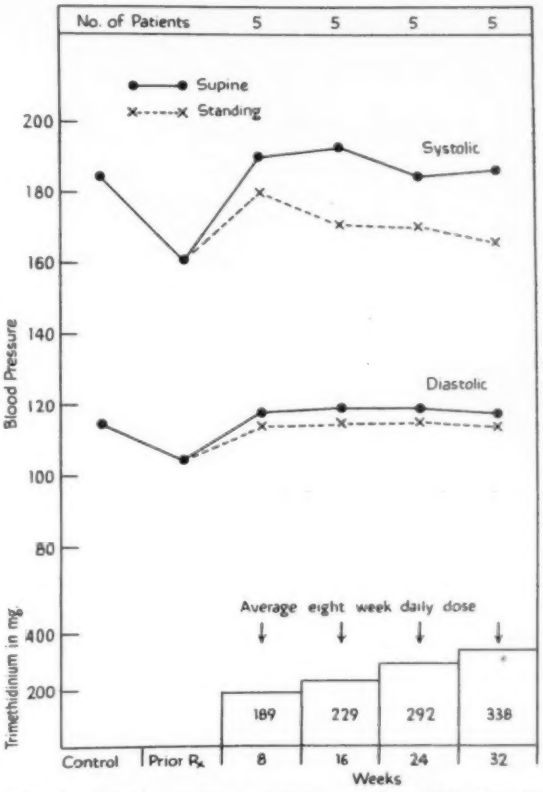

FIG. 3. Blood pressure response to trimethidinium in poor and fair response group.

mg. with the range of effective dose, 80 to 780 mg. Those same patients received an average pentapyrrolidinium dose of 533 mg., with a range of 30 to 933 mg. Thus, trimethidinium methosulfate appears approximately one and a half times more potent than pentapyrrolidinium.

Of the fifteen patients who received pentapyrrolidinium previously three patients had shown an excellent response and continued to do so during trimethidinium methosulfate therapy. Of the seven patients who had a moderate response to pentapyrrolidinium, five had an excellent response to trimethidinium while two were unchanged. Two patients had a fair response to pentapyrrolidinium; on trimethidinium one of these attained a moderate response and the other remained unchanged. A poor response to pentapyrrolidinium occurred in three patients, one of whom had an excellent response with trimethidinium while two remained unchanged.

As with oral pentapyrrolidinium therapy, a narrow therapeutic range of trimethidinium methosulfate was encountered frequently.

Tolerance to trimethidinium methosulfate developed in two patients. It occurred eight and sixteen weeks, respectively, following initiation of the drug. Although it was necessary to increase the dosage approximately 100 per cent, these two patients continued to be normotensive while receiving the medication.

Other Clinical Effects: While under the effects of trimethidinium methosulfate the patients who had diabetes did not experience untoward effects in control of their diabetes. The patients who had been treated for congestive heart failure were free of such symptoms while receiving trimethidinium methosulfate. Two of the patients were able to discontinue digitalis therapy and have continued to be free of symptoms. In one patient with angina pectoris, there was neither aggravation nor improvement. There has not been any evidence of recurrence of symptoms of cerebral artery insufficiency in the one patient who had suffered a cerebral vascular accident previously. Anxiety depression did not become worse in the three patients in whom it was present.

Side Effects: The incidence and severity of side effects are listed in Table I. There was a 5 to 20 per cent reduction of frequency and severity of the more common side effects during the final two months of the study period, al-

TABLE I
Incidence and Severity of Side Effects

Side Effect	No. of Cases	Incidence (%)	1 Plus	2 Plus	3 Plus
Constipation	15	75	15	0	0
Blurring of vision	14	70	9	4	1
Weakness	11	55	4	6	1
Dizziness	10	50	4	6	0
Dryness of mouth	9	45	7	1	1
Increased appetite	5	25	1	4	0
Postural hypotension	4	20	3	1	0
Headaches	3	15	2	1	0
Nausea and vomiting	2	10	1	0	1
Sedation	2	10	2	0	0

though constipation remained 1 plus throughout.

Further Analysis of Blood Pressure Response: As judged by the severity index two cases of severe hypertension became moderate after therapy with trimethidinium methosulfate. Of the fifteen cases of moderate hypertension, nine became mild while the rest remained in the moderate group. Three cases of mild hypertension remained the same after therapy with trimethidinium methosulfate.

Although the severity of the hypertensive disease in our patients is somewhat less than that reported in similar studies,[8–12] our patients received an average daily dose of pentapyrrolidinium that was one and three-fourths of that reported by others[10–14] in obtaining similar reduction of blood pressure. A comparison of this group with those reported in the literature is probably valid.

The administration of trimethidinium methosulfate resulted in a significant reduction in the pretreatment blood pressure levels in seventeen of twenty patients so treated. Of the seventeen patients who showed a response to the medication eleven became normotensive in the erect position; of the six patients who demonstrated a response but failed to become normotensive, three had episodes of postural hypotension which prevented administration of a greater dosage of trimethidinium methosulfate. Of the three remaining patients, two had complicating diseases which prevented sustained increase in dose and achievement of normotensive levels; although no side effects developed in the third, a reduction in blood pressure to normotensive levels was not attempted since it was thought undesirable in this particular case. There are three patients listed as having a poor response. Two of these became normotensive with additional medication although they are classified as poor results because the dosage of trimethidinium methosulfate was limited by definite or suspected side effects. The third patient had a poor response because the medication produced nausea and vomiting before effective therapeutic levels could be reached.

The average pretreatment blood pressure level was 198/122 mm. Hg for our twenty patients. Following the administration of trimethidinium methosulfate the blood pressure level for this group of patients was 141/95 mm. Hg in the standing position and 168/104 mm. Hg in the supine position.

Comparison of Trimethidinium Methosulfate, Pentapyrrolidinium and Mecamylamine: The average blood pressure recorded in the standing position for the fifteen patients treated with pentapyrrolidinium was 158/102 mm. Hg. When the same fifteen patients were treated with trimethidinium methosulfate, the average blood pressure was 143/94 mm. Hg. Consideration must be given to the fact that pentapyrrolidinium in some cases was not given to the point of its maximum effect. On the other hand, the average dose of pentapyrrolidinium used in our cases is about one and three-fourth times the average dose used by other investigators to secure similar results.

Utilizing a method similar to the present study, Page[12] compared the effect of mecamylamine with that of pentapyrrolidinium and noted a greater reduction in blood pressure in thirteen of twenty-two patients, while in two patients it remained the same and in six it became higher. In our patients who were shifted from pentapyrrolidinium to trimethidinium methosulfate therapy, a corresponding effect was achieved in which the blood pressure was lowered in seven of fifteen patients and unchanged in the remaining eight. It appears that the hypotensive effect of trimethidinium methosulfate and mecamylamine is about the same; however, none of the patients treated with trimethidinium methosulfate showed an increased blood pressure whereas almost one-third of the patients treated with mecamylamine were adversely affected.

The reduction in blood pressure with the use of mecamylamine as reported by both Freis[9] and Moyer[11] was similar to that achieved by us with trimethidinium.

TABLE II

Severity Indices* Before Treatment, after Pentapyrrolidinium Therapy and after Methidinium Methosulfate Therapy, Arranged According to the Response to the Latter

Case No.	Classification			Response
	Before Treatment	After Pentapyrrolidinium	After Methidinium Methosulfate	
1	12, moderate	5, mild	3, mild	Excellent
2	11, moderate	15, severe	9, moderate	Excellent
3	11, moderate	11, moderate	6, mild	Excellent
4	11, moderate	10, moderate	9, moderate	Excellent
5	10, moderate	10, moderate	5, mild	Excellent
6	10, moderate	9, moderate	9, moderate	Excellent
7	9, moderate	...	7, mild	Excellent
8	9, moderate	8, moderate†	7, mild	Excellent
9	8, moderate	6, mild	4, mild	Excellent
10	8, moderate	7, mild	7, mild	Excellent
11	7, mild	3, mild	3, mild	Excellent
12	15, severe	...	10, moderate	Moderate
13	15, severe	12, moderate	9, moderate	Moderate
14	10, moderate	9, moderate	9, moderate	Moderate
15	8, moderate	8, moderate	8, moderate	Moderate
16	9, moderate	8, moderate	7, mild	Fair
17	9, moderate	...	6, mild	Fair
18	10, moderate	...	4, mild	Poor
19	1, mild	3, mild	5, mild	Poor
20	1, mild	3, mild	3, mild	Poor
Average	9.2, moderate	8, moderate	6.5, mild	

* Classification of hypertension is by Goodyer's[7] criteria, in which a severity index of 1 to 7 is mild, 8 to 13 moderate, 14 to 20 severe and 21 or greater malignant.

† On mecamylamine.

Associated Drug Therapy: Two patients with a poor response to trimethidinium methosulfate therapy achieved an excellent response when other hypotensive drugs were added to their regimen. In one case normotensive levels were achieved by the addition of 500 mg. of chlorothiazide twice daily and in the other, by the addition of 50 mg. of hydralazine four times daily. These ancillary medications allowed the use of smaller doses of trimethidinium methosulfate with marked diminution in side effects and the attainment of a previously unachieved excellent reduction in blood pressure.

Four patients who also received hydralazine (200 to 400 mg. daily) throughout this study received an average dose of 178 mg. of trimethidinium methosulfate as compared with an average dose of 334 mg. for the remainder of the patients in the series. Three of the four patients who received hydralazine were in the excellent response group. While this is not a significant number of patients, it appears that the addition of hydralazine results in a more favorable response with a smaller dose of trimethidinium methosulfate. Eleven patients received only trimethidinium methosulfate, while five patients received trimethidinium methosulfate and reserpine in combination, the dosage of the latter varying from 0.5 to 1 mg. per day. The addition of reserpine to the regimen did not significantly affect the average dose level or the expected response. No conclusion can be drawn since the number of patients is small. However, in another study of trimethidinium methosulfate and reserpine, the investigators[8] found that this combination of drugs produced a synergistic effect.

In a recent report concerning the use of trimethidinium methosulfate, Dunsmore et al.[8] noted a satisfactory response while using an average dosage of only 158 mg. daily. In our series it was necessary to employ more than twice this amount to obtain equivalent results. Over 60 per cent of their patients were classified as

Smithwick 4, whereas none of our patients were in this category. The average age of their patients is not listed for comparison. It is noted that all but one of their patients received their medication three times per day, while over one-third of our patients obtained adequate response with two doses daily. It is doubtful that this difference in plan of administration would alone produce this great discrepancy in the average dose. Presumably the difference is in the patients. Dunsmore's group[8] also noted a period of tolerance shortly after initiating therapy with trimethidinium methosulfate which did not appear in our patients.

SEVERITY INDEX

Before the initiation of therapy the severity index graded 75 per cent of the patients as having moderate hypertensive disease, 15 per cent mild and 10 per cent severe (Table II). The severity index during the control period was 9.2 (moderate); at the conclusion of therapy with pentapyrrolidinium 8 (moderate); and at the time of this report while on trimethidinium 6.5 (mild).

The decrease in the severity indices after therapy with trimethidinium methosulfate was slightly greater than that after therapy with pentapyrrolidinium, although the average time on trimethidinium methosulfate was thirty-five weeks compared to two years on pentapyrrolidinium. Most of the reduction in indices is due to changes in blood pressure, although in two cases the decrease was due to control of cardiac failure and in one case, to improvement in retinopathy from grade 4 to 1. Four patients who were in heart failure before receiving trimethidinium methosulfate became asymptomatic and two no longer required digitalis.

SIDE EFFECTS

Constipation, blurring of vision, weakness and dizziness were the most common side effects seen with trimethidinium methosulfate therapy (Table I). Of the patients experiencing constipation, eight required Prostigmin at least once daily; three others used it less frequently.

Usually, blurring of vision was transient, lasting for periods up to two to three weeks, after which accommodation improved. This symptom did not correlate with the dose of the drug, or with the response of the blood pressure to the drug.

Weakness was usually associated with lowering of blood pressure and generally decreased considerably as lower blood pressures were maintained. Dizziness in four patients was a side effect of trimethidinium methosulfate administration but in the other six the cause could not be ascertained. It was usually seen with changes of position, particularly from the supine to the erect. Syncope did not occur.

Severe dryness of the mouth occurred in only two patients and was not necessarily related to the dose. Tachycardia was not seen in our patients. Nausea and vomiting were seen in two cases and resulted in the reduction of the total daily dose in one, and cessation of therapy with this drug in the other.

Sedation was experienced at the time of lowering of blood pressure, but was not a problem that required reduction in dose. Of the patients who reported increased appetite only two experienced a mild increase in weight. Impotence and decrease of libido were not adequately evaluated; it was a complaint in two patients who are not included in this report because of inadequate attendance at the clinic.

Side effects usually disappeared or became insignificant after a short period of adjustment to lowering of blood pressure. The development of more severe side effects at a dosage inadequate to control the blood pressure was the limiting factor that resulted in a poor or fair response. There was a direct relationship between the total daily dose and the frequency, severity and duration of side effects. Patients receiving 300 to 500 mg. of trimethidinium methosulfate daily were apt to show transient side effects of a limited nature, whereas patients receiving a total daily dose of 500 mg. and more of trimethidinium methosulfate usually experienced more severe side effects.

The incidence and severity of side effects of trimethidinium were compared to those experienced by Fries et al.[13] with pentapyrrolidinium. With the use of trimethidinium blurring of vision occurred only one-third as often. Constipation due to administration of trimethidinium was always controllable with Prostigmin, whereas 15 per cent of those receiving pentapyrrolidinium were uncontrolled with neostigmine. Syncope did not occur in our group, whereas 4 per cent in this comparable group had this symptom.

In a similar comparison with mecamylamine, blurring of vision was more frequent but less persistently bothersome with trimethidinium while constipation was about the same frequency but much less severe.

The incidence of constipation in our series is much greater than the 5.3 per cent reported by Dunsmore et al.[8] A likely explanation is that their average daily dose was 157.8 mg. as compared with 334 mg. for our patients. It is to be noted that the comparison of the severity of constipation is difficult to evaluate due to lack of clarity of its gradation in all the reported series which we reviewed dealing with hypotensive therapy with ganglionic blocking agents.

Summary

Trimethidinium methosulfate, a new vasodilator drug which acts through its ganglionic blocking effect and through central action, was tested in twenty patients with hypertension for an average period of nine months. Trimethidinium methosulfate produced a significant response in 85 per cent of the cases, 55 per cent becoming normotensive. The reduction in the average blood pressure levels was 57 mm. Hg systolic and 27 mm. Hg diastolic. Since most of the patients had been treated previously with pentapyrrolidinium it was possible to compare the two drugs. Trimethidinium methosulfate showed a better and more consistent hypotensive effect, greater and more rapid reduction in severity index, and although side effects were more frequent, they were less severe and more easily controlled. Comparison of the results with trimethidinium with those reported in the literature for pentapyrrolidinium and mecamylamine shows the control of blood pressure to be at least as good or better and the side effects to be less severe and more manageable.

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Reviews

Transmembrane Cationic Gradient and Blood Pressure Regulation

Interaction of Corticoids, Catecholamines and Electrolytes on Vascular Cells*

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CONTRARY to beliefs and creeds now outdated, the blood pressure level and its fluctuations are not determined by one single organ system, such as the central nervous system, the endocrines or the kidneys, but by complex interactions of all of these. The patterns of their subtle interplay vary not only from person to person but also within the same individual, in an incessant, partly rapid, partly slow succession of regulatory adjustments to extraneous and internal situations.

The present review is not primarily concerned with the mutual interrelation of those high level organic forces which form the general background of blood pressure reactions. It is rather intended to point out certain basic regulatory mechanisms at the vascular cellular level under hormonal-neurohormonal influences, and their pathogenic as well as therapeutic implications.

CORTICOIDS POTENTIATE PRESSOR EFFECTIVENESS OF CATECHOLAMINES

In 1942, a striking potentiation of pressor catecholamine effectiveness by corticoid action was demonstrated by the writer[123] on human volunteer subjects (Fig. 1). Pretreatment with desoxycorticosterone acetate (DCA) markedly intensified the pressor effect of epinephrine. The same phenomenon was later shown[137] to apply likewise to norepinephrine, concerning both the systolic and diastolic pressures (Fig. 2).

DCA-induced intensification of pressor catecholamine action was confirmed by Sarre[155] in man, by Vanatta et al.[192,193] in dogs, by Friedman and Friedman,[47] and by Gross and Lichtlen[68b] in rats. In rats with DCA-hypertension, Masson, Page and Corcoran[100] found the pressor effect of epinephrine only irregularly and slightly elevated but, according to calculation by Vanatta and Cottle,[192] the deviations were statistically significant. Croxatto et al.[20] failed to notice alteration of epinephrine response after implantation of DCA pellets. The contractile reaction of isolated aortic strips to epinephrine was seen to be potentiated by DCA,[5a] in contrast to observations by Mallov.[95b]

Sensitization of the vascular system to constrictor catecholamine action has been observed not only under the influence of DCA but also under that of cortical extracts in cats[111] and adrenalectomized dogs,[143] and after administration of cortisone[87,102b] and hydrocortisone[96] in human subjects. Moreover, it was elicited by cortical extracts on the mesenteric vessels of the adrenalectomized rat.[52] Combination of DCA with cortisone did not significantly alter the catecholamine-potentiating action of the former.[142]

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On the other hand, the pressor effect of epinephrine has been described as being reduced in Addison's disease,[130] and that of both epinephrine and norepinephrine after experimental adrenalectomy.[14,143,146,147] According to Salmoiraghi and McCubbin,[153] the responses to epinephrine and norepinephrine were diminished only in the terminal stage of adrenal insufficiency. In other experiments, norepinephrine failed to constrict the mesenteric vessels[52] after adrenalectomy. In adrenalectomized cats, the blood pressure elevations accompanying stimulation of peripheral nerves were reduced or extinguished[147,163] but could be restored to normal through administration of an adrenal cortical extract.[163]

Whereas McQueen[102a] found the isolated vessels from rats with renal ischemia over-reactive to norepinephrine, no differences in the norepinephrine reactivity were observed by Redleaf and Tobian[144] in aortic strips from rats with various types of hypertension, including that induced by DCA. (In these latter experiments, the vessels had first been bathed in nitrites for complete relaxation, which may have deprived them of their specific hypertension-producing biochemical qualities.) Redleaf and Tobian,[144] although not unduly stressing the analogy of aortic reactions with those of the small arterioles, nevertheless question the corti-

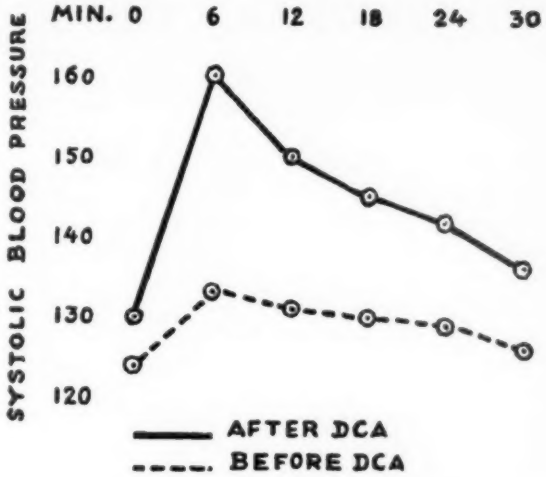

FIG. 1. Potentiation of systolic blood pressure effect of epinephrine (0.4 to 0.5 mg. administered subcutaneously) after pretreatment with desoxycorticosterone acetate (DCA) (average daily dose 25 mg. for an average of five days). Average effects in six cases.[123]

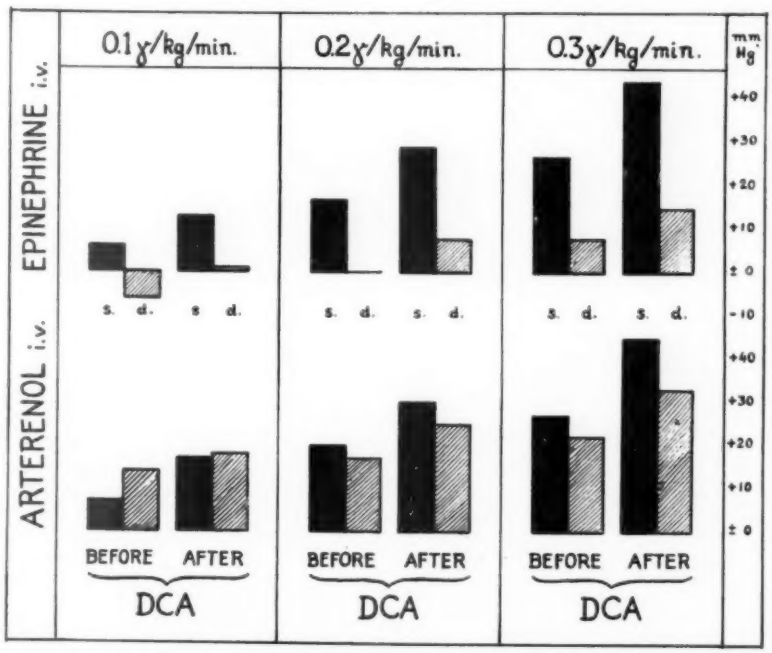

FIG. 2. Potentiation of pressor effects of mounting doses of intravenously infused epinephrine and norepinephrine (arterenol) by pretreatment with DCA (black areas are deviations from systolic, shaded areas are deviations from diastolic resting blood pressure levels). Dose of DCA, 10 mg. daily during average of seventeen days in fifteen cases. Average blood pressure before DCA, 136/81 mm. Hg; after DCA, 139/85 mm. Hg. (From: RAAB, W. et al. *J. Clin. Invest.*, 29: 1397, 1950.[137])

coid-induced augmentations of pressor catecholamine effects as being caused by a real vascular constrictor over-reactivity. Instead, they suggest as possible factors a primary narrowing of the vascular lumen due to either "water-logging" of the vascular walls or to a pre-existing state of hypertension-producing contraction. The latter interpretation may apply to some of the experiments of those[28,95b,176] who found pressor and local vasoconstrictor catecholamine effects exaggerated in various types of existing hypertension. However, Sturtevant[176] and Gross and Lichtlen[68b] emphasize that the pressor reactions were not related to the blood pressure level before injection. The same holds true for the markedly overshooting catecholamine effects which we have observed, starting from still normal blood pressure levels, in human subjects treated with DCA[123] and in non-hypertensive pregnant women before the development of toxemia,[141] and which others have described in rats which, despite treatment with DCA, were still normotensive.[47]

The blood pressure of animals with DCA- or metacorticoid-hypertension could be lowered by procedures which diminish the vascular adrenergic neurohormone supply either through ganglionic blockade[175] or through catecholamine-destroying reserpine.[53,175] This indicates the participation of a neurogenic element in corticoid-induced types of hypertension. The same is also suggested by the fact that the presence of an active thyroid gland proved necessary to permit the development of DCA-hypertension,[152] since the thyroid hormone seems to precondition the cardiovascular and metabolic effects of the catecholamines.[9]

Electrolytes Mediate the Corticoid-Induced Potentiation of Pressor Catecholamine Effectiveness

After Loeb,[92] Swingle et al.[179] and Floyer[39a] had postulated an involvement of cellular electrolyte balance in blood pressure regulation, and after our experiments[138] had shown that lack of dietary sodium is accompanied by a weakening of catecholamine pressor action, as well as by an inability of DCA to restore it, the following "working hypothesis" was proposed in 1952:[129] "The intrinsic catecholamines (especially neurogenic norepinephrine) act on the contractile vascular cells as depolarizing agents and serve as physiological stimuli in the maintenance of vascular tone. Their pressor effectiveness depends on the electric membrane potential of the contractile cells which, in turn, is determined by the intra-extracellular electrolyte concentration difference, which, in turn, is influenced by the adrenal mineralocorticoids by virtue of their specific ability to deposit sodium intracellularly."

Desoxycorticosterone causes an intracellular accumulation of sodium and a gradual elevation of the blood pressure particularly if extra sodium chloride is added to the diet, whereas sodium depletion and a fall of the blood pressure occur after adrenalectomy, with severe aggravation and eventual shock when sodium intake is restricted.[130]

The importance of the intra-extracellular or transmembrane "cationic gradient" for cellular membrane potentials and muscular contractile power has been investigated extensively by Fleckenstein[38] and Shanes.[168b] It is generally agreed that in both striated and smooth muscles the membrane potential is inversely related to muscular tone and contractile responsiveness.[5a,5c,20b,38,50]

Transmembrane Sodium Ion Gradient: In 1957 Friedman and co-workers[48] presented suggestive evidence for a fundamental role of the transmembrane sodium ion gradient in blood pressure regulation. The same team of workers,[50] applying the results of *in vitro* and infusion studies to the principles of vascular tone and reactivity, arrived at the conclusion that small alterations of the intracellular sodium content correspond in their effect on vascular contractility to large changes of extracellular sodium. When intracellular sodium is abnormally augmented, the transmembrane sodium gradient diminishes and blood pressure will rise. Conversely, when intracellular sodium is depleted, blood pressure will fall. These situations seem to constitute equivalents of what happens under the influence of mineralocorticoids and of adrenal insufficiency, respectively. Furthermore, the effectiveness of vasoconstrictor agents was accentuated when the intracellular sodium concentration was relatively high, that is, when the transmembrane gradient decreased, and vice versa. In principle, these findings agree with *in vitro* studies of Bohr et al.[5a] who found the contractile response of aortic strips to epinephrine potentiated in a low sodium surrounding, and weakened when the sodium concentration of the medium was increased. Exposure of the vascular tissue to DCA likewise augmented the contractile effectiveness of epinephrine. It thus appears probable that it is

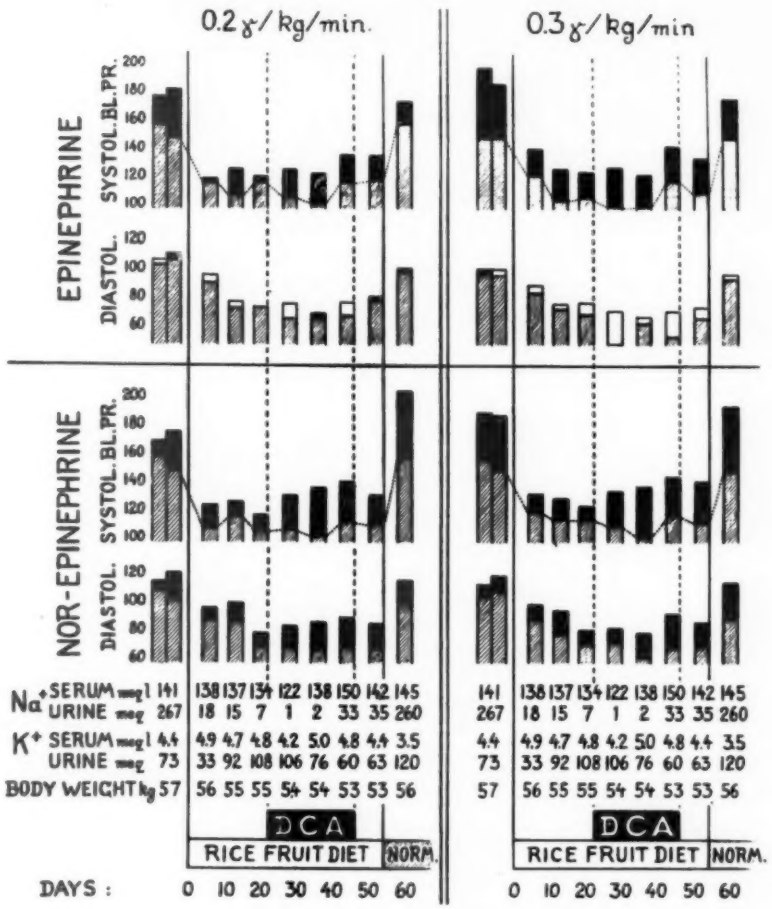

FIG. 3. Pressor effects of intravenously infused epinephrine and norepinephrine weakened by sodium-poor diet, and failure of DCA to potentiate the pressor effects until return to normal sodium-containing diet (compare with Fig. 2). The black areas indicate average elevations, the white areas average falls of blood pressure during five-minute infusions. (From: RAAB, W. et al. *Circulation*, 6: 373, 1952.[138])

mainly the intra-extracellular difference of sodium concentration (regardless of the absolute amounts present) which would account for the exaggerated pressor effect of the catecholamines after pretreatment with corticoids, and for the opposite in adrenal insufficiency.

As far as the actual sodium content of vascular tissue is concerned, it has been shown by Tobian and Binion[189] that the aortic sodium of rats with both DCA- and renal hypertension, and of deceased human beings with hypertension,[188] exceeds the normal level, apparently due to intracellular accumulation. The same was observed by other workers,[23c, 68d] in animals with early DCA-hypertension but not in those with post-DCA-hypertension. Greene and Sapirstein,[66] who found the total body sodium increased in hypertensive nephrectomized rats, likewise assume a vascular intracellular deposition of sodium.

Changes in Sodium Metabolism and Vascular Contractility: Most investigators attribute the vasopressor effects of experimentally administered or spontaneously secreted corticoids on the one hand, and the loss of vascular tone in adrenal insufficiency on the other, to changes in the sodium metabolism in general[8,17,18,49,54,63,68a,84,155,160,166,177,193] and, more specifically, to the influence of local sodium ions on the vascular contractile cells.[66,69,129,130,131,188,189,191]

Prolonged excessive alimentary intake of sodium *per se* proved sufficient in many instances, although not invariably,[202] to raise the blood pressure.[7,21,23,68a,103,154,177] By contrast,

dietary sodium restriction, without exerting any impressive influence on normal blood pressure,[186] has often proved therapeutically effective in clinical hypertension.[130] The withdrawal of sodium from the diet weakens or abolishes DCA-hypertension.[118,155,168a] Tobian[186] found the sodium concentration diminished in the aortas of normal rats fed low salt diets. However, in rats with renal hypertension, salt restriction did not substantially reduce the vascular sodium concentration, nor did it lower the blood pressure.[145] Only maximal salt depletion by means of withdrawal plus peritoneal lavage brought the blood pressure to normal.[44] It is not known whether alterations of exogenous sodium affect the intra-extracellular sodium gradient of vascular muscle cells directly or also by influencing the formation and secretion of corticoids from the adrenal glands.

The stubborn sodium retention by animals with renal hypertension and the frequent ineffectiveness of therapeutic sodium restriction in clinical hypertension would seem consistent with the hypothesis concerning a significant renal retention of sodium-preserving corticoids,[46] were it not for the fact that even adrenalectomy not infrequently fails to normalize both experimental "metacorticoid"[64] and clinical hypertension.[6,81] In such instances, the development of permanent structural changes of the arterioles (hypertrophy) must be considered as a possible factor.[39b] Electron microscopic studies of the vascular walls, as proposed by Backer,[10] may help to clarify the question of basic cellular anomalies in the origin of hypertension.

A direct relationship between sodium intake and catecholamine sensitivity has been suggested by our demonstration[138] of a weakened pressor effectiveness of infused epinephrine and norepinephrine, as well as of a reduced ability of DCA to restore these effects, during prolonged severe salt restriction in patients with mild hypertension (Fig. 3). The impairment of the pressor action of norepinephrine by withdrawal of salt could not be regularly duplicated by Dahl[22] in human subjects, or by Tank and Herin[181] in the dog. (It may be mentioned in this connection that dogs proved equally unsuited for the development of plain salt hypertension,[202] as well as of combined DCA-salt hypertension.[178]) Isolated vessels of salt-fed rats, on the other hand, did display an exaggerated contractile reaction to epinephrine,[196,207] whereas dietary sodium deficiency produced a diminished response to epinephrine.[207] The sodium-depleting diuretic agent chlorothiazide was found to reduce the pressor effectiveness of epinephrine and norepinephrine.[120b] Hydrochlorothiazide has the same effect and inhibits DCA-hypertension.[3b,68c] As far as the depressor and catecholamine-desensitizing sequelae of plain dietary sodium withdrawal are concerned, it seems possible that a diminution of total corticoid production under such a regimen[119] may serve as a contributing factor, even though aldosterone production is augmented.[91b]

Potassium and Vascular Contractility: Beside the evidence in favor of profound involvement of cellular sodium exchange in the cardiovascular action of corticoids, and of its importance for vascular reactivity to adrenergic catecholamines, it has been pointed out by Freed, Rosenman and Friedman[41] that similar principles likewise apply to alterations of the body's supplies of potassium.

Deficiency of potassium was found to depress the basic blood pressure level, to weaken the pressor effects of epinephrine and norepinephrine, and to inhibit the development of DCA-hypertension.[41,117] However, the pressor effectiveness of DCA *per se* (which inhibits the entry of potassium into the cells,[19,70,174]) was not potentiated by feeding of potassium[149] in contrast to feeding of sodium (see preceding section). Cortisone (but not DCA) restored the hypotension induced by potassium deficiency to normal.[41,150]

Interestingly, the simultaneous reduction of dietary potassium and sodium failed to lower the blood pressure level.[40] An increase of the dietary sodium/potassium ratio was followed by a paradoxically depressant effect of DCA.[149]

In the aortic walls of animals with severe hypertension, Tobian and Redleaf[191] found an augmentation of water, sodium and potassium while in those with early and mild DCA-hypertension only sodium was increased and potassium diminished.[23c,187,191] Other workers[41b,68d] observed an augmented potassium concentration in the tissue of the aorta.

Bohr et al.[5a] studied the response of isolated aortic strips to DCA and catecholamines in a changing electrolyte medium. A decrease of the potassium gradient (through addition of KCl to the bath) was accompanied by potentiated vascular contractile response to epinephrine, whereas accentuation of the potassium gradient weakened reactivity to epinephrine.

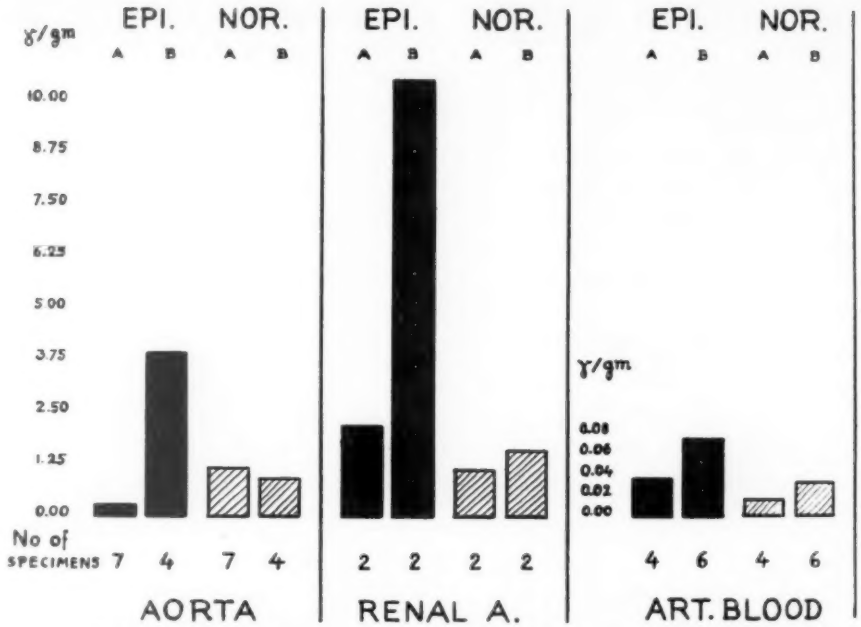

FIG. 4. Epinephrine (black) and norepinephrine (shaded) in arterial walls and blood of dogs before (A) and after (B) intraperitoneal injection of epinephrine (10 mg./kg.). By contrast to striated muscle, arterial walls and heart muscle absorb and store catecholamines from the circulating blood. (From: RAAB, W. and GIGEE, W. *Angiology*, 9: 283, 1958.[138])

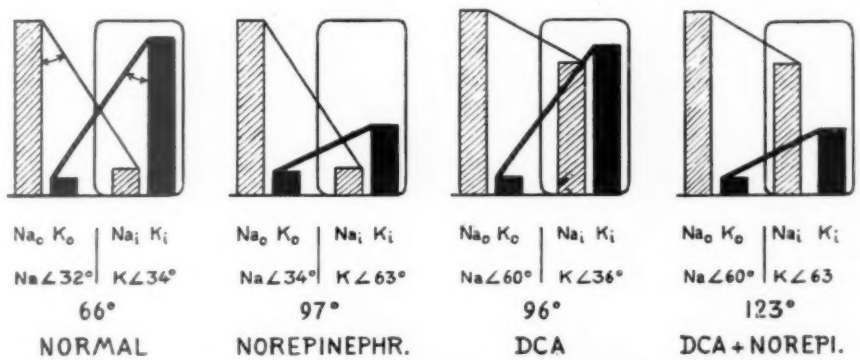

FIG. 5. Schematic representation of transmembrane gradients of extra-intracellular sodium (Na_o/Na_i) and intra-extracellular potassium (K_i/K_o). The dimensions are arbitrary. (Approximate real values are:[38] Na_o = 148 mM/kg.; Na_i = 15.8 mM/kg.; K_i = 105 mM/kg.; K_o = 4.5 mM/kg.) The gradient angles are equally arbitrary, and the corresponding figures are intended merely to symbolize the principle of an increase of contractility, resulting from a diminished gradient for each cation, reaching a maximum if both gradients (of Na^+ and K^+) are reduced (e.g., potentiation of contractile catecholamine effectiveness after pretreatment with DCA; see Figs. 1 and 2).

Norepinephrine infusion was found to deplete the tissue of the aorta[23d] and of the femoral artery[190] of much of its potassium content, sometimes in association with small gains of sodium.[190]

Corticoids, Catecholamines and Vascular Contractility: The constant presence of catecholamines in the vascular walls has been demonstrated by ourselves[124] and by others. They consist prevailingly of norepinephrine,[12,82,135,158] but circulating epinephrine is also avidly absorbed and deposited by vascular tissue[135] (Fig. 4).

A survey of available data concerning the significance of corticoids and catecholamines for vascular tonus and reactivity seems to corroborate our original hypothesis that the interaction of these powerful pressor agents is effectuated by their respective integrated influences on the transmembrane gradients of sodium and

potassium. The "mineralocorticoids" (DCA and aldosterone) seem to act chiefly by way of a relatively slow intracellular accumulation of sodium, whereby the transmembrane sodium gradient is decreased (Fig. 5) and the vascular tone and contractile responsiveness are accordingly augmented. The behavior of intracellular potassium under the influence of DCA proved somewhat irregular. There are some indications that cortisone and hydrocortisone are more intimately concerned with cellular potassium exchange but direct evidence for this is still lacking.

The catecholamines cause a rapid extrusion of intracelluar potassium, thus presumably diminishing the transmembrane potassium gradient with a resulting increase of contractility. Both features, the corticoid-induced and the catecholamine-induced diminutions of the sodium and potassium gradients, would account jointly for the potentiation of catecholamine pressor effectiveness by mineralocorticoid action on the vascular cells (Fig. 5).

On the basis of Fleckenstein's classic investigations,[38] we had originally assumed that the influence of the transmembrane cationic gradient on vascular tone and catecholamine sensitivity is mediated by corresponding alterations of the electrical cell membrane potential. However, since neither Bohr et al.[5b] nor Daniel et al.[23e] were able to demonstrate *in vitro* any externally recordable action potentials in association with epinephrine-induced vascular contraction, and since the latter occurred also after artificial depolarization of the cell membrane, it was concluded that the epinephrine response of the vascular cells may be dissociated from the process of membrane depolarization, and may rather be caused by a change in membrane permeability and resulting alterations of intracellular environment, possibly facilitating the transfer of energy from ATP to actomyosin.[5b] The action of norepinephrine, the intrinsic vascular neurohormone, which, in contrast to epinephrine, is an "over-all vasoconstrictor"[58] and much more important with regard to the hypertension problem than epinephrine, has apparently not yet been investigated concerning its depolarizing properties, if any.

Pathogenic Implications

The previously outlined principles of corticoid-induced, electrolyte-mediated sensitization of the vascular system to the constrictor effects of intrinsic and extrinsic catecholamines can obviously be applied to the primarily neurogenic (i.e., neurohormonal) and the primarily hormonal forms of hyper- and hypotension (Table I).

Clinical Neurohormonal and Neurogenic Pressor Mechanisms

The terms "neurohormonal" and "neurogenic" hypertension embrace all types of absolutely or relatively exaggerated action of pressor catecholamines upon the vascular walls (Fig. 6). The paroxysmal or sustained elevations of blood pressure in patients harboring a pheochromocytoma represent the most unequivocal example of hypertension due to catecholamine overproduction and overaction. A more diffuse and less conspicuous exaggerated discharge of norepinephrine as the specific humoral transmitter from the sympathetic nerve terminals into the muscle cells of large vascular areas may be assumed to result from central or peripheral stimuli which affect the vascular sympathetic nerve supply.[58]

The process of neurosecretion into the vascular tissue is technically difficult to demonstrate but the constant presence of norepinephrine and epinephrine in the arterial walls[12,82,124,135,158] (Fig. 4), testifies to its existence. Its enhancement under certain circumstances may be inferred indirectly from the increase of myocardial norepinephrine after electrical stimulation of the cardiac sympathetic nerves,[134] from the depletion of catecholamines in stimulated postganglionic sympathetic fibers,[34,136] and also from the appearance of increased amounts of norepinephrine in the urine under emotional stress,[32,114b] and in the blood[61,93,126,148] and urine[83] during physical exercise.

Pathologic central excitations of the sympathetic nervous system are elicited by injury, concussion, infection, vascular ischemia of central vasoconstrictor areas, increase of intracranial pressure and the like.[130] Moreover, many somatic as well as intracerebral (emotional) reflexes contribute to pressor nervous stimulation[104,169] (Fig. 6). A relative adrenergic preponderance, resulting from a functional deficiency of the vascular baroceptor cholinergic mechanisms, is assumed to develop in cases of sclerotic nondistensibility of the carotid sinus,[198] in apparent analogy to Wakerlin's[200] experiments with constriction of the carotid sinus.

The seemingly paradoxic persistence of strong centrogenic pressor reflexes after total sympathectomy[2,42,67] suggests the possibility that

TABLE I—Summary of Presumed Clinical Pressor and Depressor Mechanisms and Therapeutic Implications in Various Types of Hypertension and Hypotension

Type of Blood Pressure Anomaly	Pathogenic Background	Corticoids Acting on Electrolyte Gradient	Catecholamines Acting on Electrolyte Gradient	Abnormal Renal Pressor Agents	Presumed Changes of Transmembranous Electrolyte Gradient		Deviation of Blood Pressure	Rational Therapy
					Na_o/Na_i	K_i/K_o		
None	None	+	+	—	Normal	Normal	None	None
Primary hormonal hypertension	Adrenal cortical tumors or hyperplasia, pregnancy (toxemic)	+++ (++)	+	— (+)	Decrease	Normal	↑	Removal of adrenal cortical tissue; salt withdrawal, natriuresis*
Primary neurohormonal (neurogenic) hypertension	Pheochromocytoma, cerebral injury, tumor or infection	+	+++ (++)	— (+)	Normal	Decrease	↑	Removal of tumor; treatment of cerebral disease
"Essential" hypertension	Centrogenic emotional, reflex; cerebral vascular ischemia; insufficiency of vascular baroceptors; secondary renal vascular pathology	+ (++)	++ (+)	(+)	Normal or decrease	Decrease or normal	↑	Psychotherapy; ganglionic blockade; reserpine; natriuresis;* hydralazine
Renal hypertension	Renal disease (infection; corticoid-catecholamine induced); retention of catecholamines, corticoids (?)	+ (++)	+ (++)	++ (+++)	Normal or decrease	Normal or decrease	↑	Treatment of renal disease; Na restriction and/or natriuresis;* ganglionic blockade; hydralazine; adrenalectomy
Hormonal hypotension	Primary hypoadrenocorticism, adrenalectomy, hypopituitarism	—	+	—	Increase	Normal	↓	Corticoid administration, extra NaCl; in emergency, norepinephrine
Neurogenic hypotension	Sympathectomy, overdosage of ganglionic blockers; centrogenic sympathetic deficiency	+	—	—	Normal	Increase	↓	Bandaging of legs, abdomen; ephedrine; in emergency, norepinephrine

* Effect possibly due to secondary diminution of total corticoid secretion, even though aldosterone production is increased.

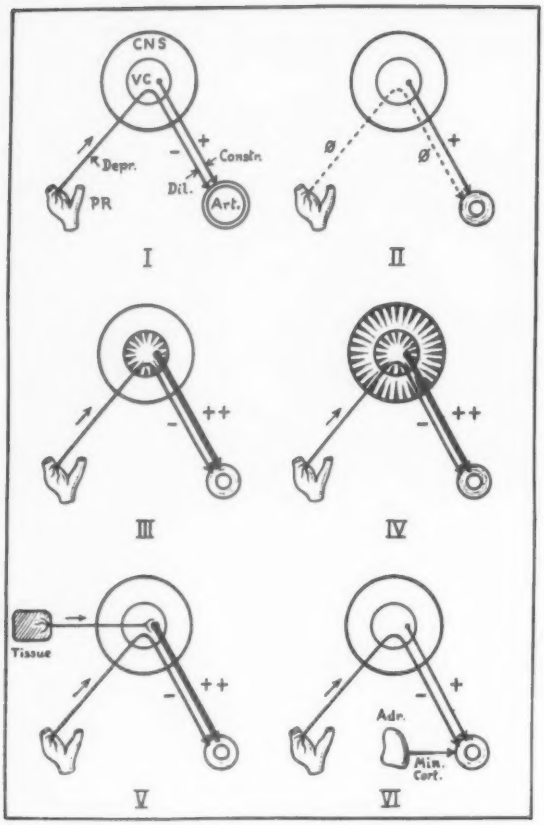

FIG. 6. *Neurogenic mechanisms of arterial hypertension.* CNS = central nervous system; VC = area of vasomotor centers; PR = pressoreceptors of vascular system; Art. = peripheral arteriole; Depr. = afferent depressor nerves which elicit parasympathetic vasodilator stimuli (Dil.) via VC; Constr. = efferent sympathetic vasoconstrictor pathways which discharge norepinephrine into the arteriolar wall cells. Their effects are normally counterbalanced by Depr.; Adr. = Adrenal cortex; Min. cort. = Mineralocorticoids. I, normal neurovegetative equilibrium—normal vascular tone. II, weakening or lack of parasympathetic reflex mechanism (e.g., due to non-dilatability of sclerotic pressoreceptor area) leaves sympathetic vasoconstrictor mechanism in control.[198,200] III, local excitation of sympathetic vasoconstrictor centers (e.g., due to local arteriolar sclerotic ischemic hypoxia and acidification,[121,122] trauma, infection, etc.) overstimulates sympathetic vasoconstrictor mechanisms. IV, central excitations originating in other areas of the CNS (emotions, conditioned reflexes) cause sympathetic pressor stimuli. V, stimuli originating in peripheral tissues (cold, pain, distencion of hollow organs) elicit sympathetic pressor reflexes. VI, adrenal cortical (mineralocorticoid) overactivity intensifies vasoconstrictor effectiveness of even normal amounts of sympathogenic norepinephrine in vascular cells (hyperadrenocorticism, toxemia of pregnancy), presumably through intracellular sodium accumulation and its effect on transmembrane cationic gradient.[129]

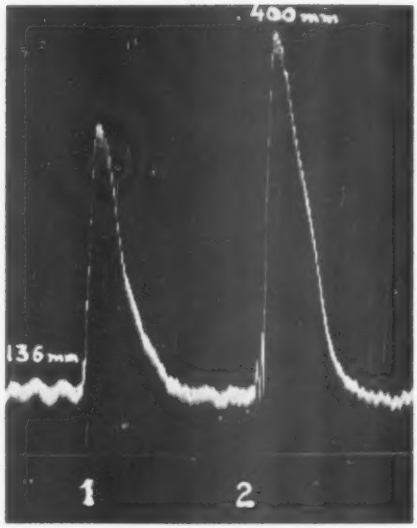

FIG. 7. Pressor effect on the atropinized cat of (1) 8 μg. of epinephrine and (2) catecholamines, extracted from 15 gm. of human brain. (From: RAAB, W. *Am. J. Physiol.*, 152: 324, 1948.[128])

vasopressor cerebral catecholamines,[128] which include norepinephrine[197] (Fig. 7), enter the general circulation and thus act on the vascular walls.

The catecholamine content of the blood of patients with early and uncomplicated "essential" hypertension at rest has been found to be within normal limits[59,104,125] (Fig. 8). This cannot be considered as proof against a moderately exaggerated norepinephrine influx into the vascular cells since these tend to absorb the catecholamines with avidity (Fig. 4), and to metabolize them rapidly.[135] During exercise, the total catecholamine level in the blood of patients with hypertension appeared to rise higher than that of normotensive people.[126] Only in cases of severe renal excretory insufficiency is the catecholamine concentration in the blood usually augmented[97,127,139] (Fig. 8), probably due to renal retention.[133] With the exception of two publications,[79,86] no abnormally large amounts of urinary catecholamines have been reported in the majority of patients with "essential" hypertension.[11,35,95,115,133]

A blood pressure-lowering depletion of the vascular catecholamine stores is to be assumed under the influence of certain derangements of the central nervous system (hypotensive states in cases of cerebral tumors, encephalitis, tabes dorsalis), after sympathetic denervation and after administration of ganglionic blocking agents,[130] again in analogy to the finding of losses of

catecholamines from the denervated heart muscle.[60,140] Reserpine causes a marked reduction of vascular catecholamines.[12] The failure of the rauwolfia drugs and of other means of vascular catecholamine depletion to depress the vascular tone more drastically than one might expect, is to be understood on the basis of Cannon's "law of denervation": an increased sensitivity of the denervated catecholamine-depleted vessels to even minute amounts of remaining vasoconstrictor material.[12]

The "permissive" role of normal adrenal cortical activity in safeguarding vascular sensitivity to catecholamine action seems to constitute an important prerequisite for the full effectiveness of all neurogenic pressor phenomena (see section on pressor effectiveness of catecholamines).

CLINICAL ADRENOCORTICAL PRESSOR MECHANISMS

The significance of a *primary overproduction of adrenal cortical hormones, notably of mineralocorticoids*, as a "conditioning" factor in the frequent occurrence of arterial hypertension in cases of cortical tumors or hyperplasias (Cushing's syndrome, "primary aldosteronism")[17,18] is well established.[130]

Toxemia of Pregnancy: Furthermore, there are increasing indications that the hypertension in toxemia of pregnancy is likewise caused by an augmented activity of sodium-retaining corticoids. This is suggested by an increased excretion of such corticoids,[13,94a,114a,185,195] by a diminished sodium content of the saliva[141,172] (Fig. 9), by urinary sodium retention,[26] by evidence of an abnormal intracellular sodium accumulation,[89,113] and by a potentiated pressor effectiveness of norepinephrine, epinephrine[141] (Fig. 9) and other pressor agents.[10,27] This latter phenomenon manifests itself in the pretoxemic stage (twenty-eighth to thirty-fourth week) when the resting blood pressure is still within normal limits (Fig. 9). An excessive pressor response to infused norepinephrine in the absence of other clinical signs has been found by us to permit the prediction of impending toxemia[132] (Fig. 10).

The nature of the steroids responsible for these abnormal features in toxemia is not yet clarified. An increased production of aldosterone has been claimed by some[94a] but disclaimed by others.[98,194] Abnormalities in the quantitative mutual relation ship of sodium-retaining and excreting steroids,[98] and an inhibition of steroid degradation,[15] have been considered hypothetically.

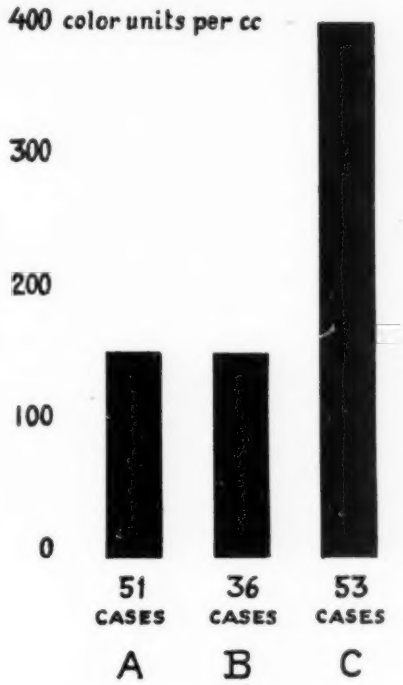

FIG. 8. Average total catecholamines in the blood of (A) normotensive subjects, (B) patients with uncomplicated hypertension and (C) patients with hypertension and renal excretory insufficiency. (From: RAAB, W. et al. *Circulation*, 14: 614, 1956.[139])

Essential Hypertension: Even more problematic is the question of a possible participation of adrenal corticoids in the pathogenesis of "essential" hypertension. Numerous attempts to reach definite conclusions from the morphologic appearance of the adrenal cortex have failed.[130] However, the finding of an increased lipid content of the adrenal cortex in cases of hypertension[75,88] seems to deserve further study. Older reports concerning an augmented excretion of corticoids in the urine were controversial.[24,74,119,164,180,185] More recently, Genest et al.[55] have reported an increased aldosterone excretion in 55 per cent of a series of patients with hypertension. According to Conn,[16] the value of assay of aldosterone in the urine is limited because not even 1 per cent of administered aldosterone can be recovered.

Since the salivary sodium concentration reflects adrenocortical activity, the finding of low average sodium values in a group of patients with hypertension was interpreted by Niedermeier et al.[108] as indicating a generally increased production of mineralocorticoids.

Using the sodium content of thermal sweat as a

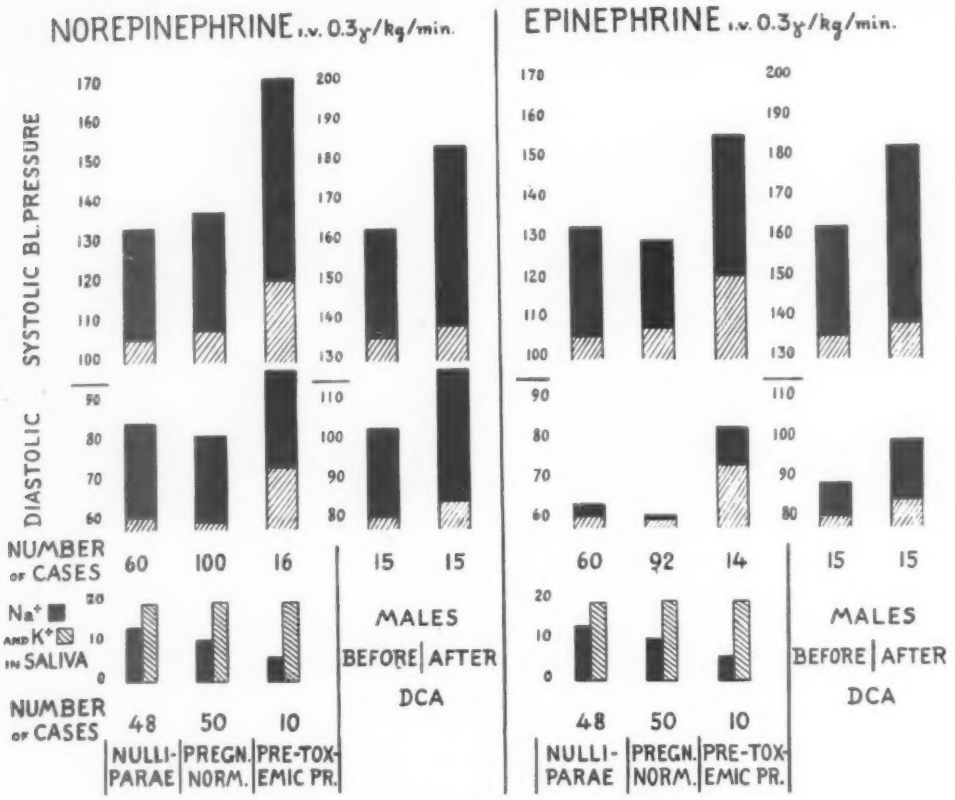

FIG. 9. Intensified pressor reactions to norepinephrine and epinephrine in normotensive, pretoxemic women (in whom toxemia subsequently developed), compared with those in nulliparous and in normal pregnant women, and with similarly intensified pressor reactions in fifteen normal males pretreated with DCA. The average salivary sodium was somewhat reduced in normal pregnancy but was maximally reduced in pretoxemia. (From: RAAB, W. et al. *J. Clin. Endocrinol.*, 16: 1196, 1956.[141])

criterion, Eisenberg, Buie and Tobian[31] did not arrive at any positive results. Davies and Clark[25] observed a diminution of sweat sodium, combined with other clinical signs of cortical overfunction ("pseudo Cushing syndrome"[161]) in about 20 per cent of a series of patients with hypertension.

The average plasma sodium levels of patients with essential hypertension have been reported as being often slightly elevated.[1a,78,201]

An augmented excretion of sodium by patients with hypertension, especially after intravenous administration of saline,[76,77,201] has been attributed to hemodynamic mechanisms rather than to direct hormonal action on sodium metabolism.[76,201]

The observation of an exaggerated constrictor responsiveness of peripheral vessels to epinephrine[28] and of an augmented pressor effect of norepinephrine in people with hypertension[58] may be caused, in part, by corticoid-induced vascular sensitization (see section on pressor effectiveness of catecholamines).

Goldberger,[57] referring to the stimulatory influence of a diminished extracellular fluid volume on aldosterone excretion[4] and to observations suggesting an increased diversion of circulating blood into the muscles of the extremities,[120a] postulates an augmented secretion of aldosterone on that basis.

Hypotension of Addison's Disease: By contrast to the scarcity of data that would suggest more than a merely "permissive" role of the adrenal cortex in the pathogenesis of essential hypertension,[16] the abnormally low blood pressure levels characterizing Addison's disease are clearly due to adrenal cortical insufficiency and, presumably in large measure, to its inhibitory effect on the responsiveness of the vascular walls to their intrinsic norepinephrine supply (see section on pressor effectiveness of catecholamines). The fact that in some in-

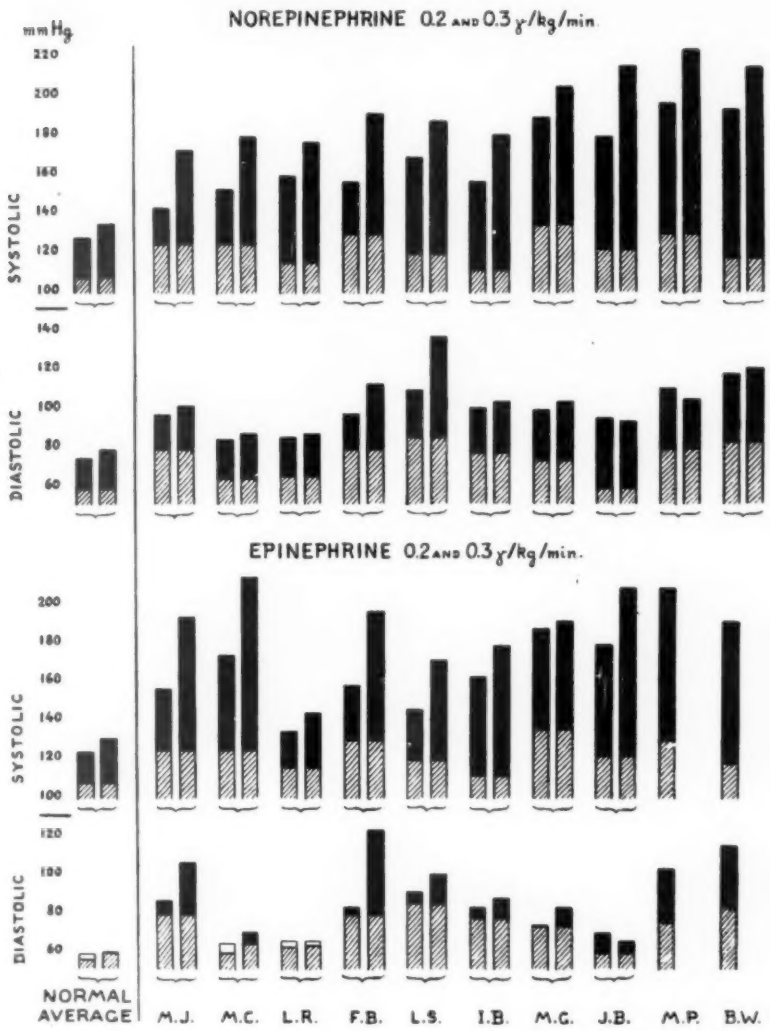

FIG. 10. Individual pressor reactions to intravenously infused norepinephrine and epinephrine (for five minutes each) in ten normotensive women in whom toxemia and hypertension subsequently developed, compared with average reactions of fifty normal pregnant women. (From: RAAB, W. et al. *J. Clin. Endocrinol.*, 16: 1196, 1956.[141])

stances of pre-existing hypertension a superimposed Addison's disease lowered the blood pressure only to near normal levels,[33,72,116] may be explained by the assumption of a continuing renal pressor mechanism, and corresponds to the mode of reaction of therapeutically adrenalectomized patients with severe hypertension.[6,81,184]

Postural hypotension, a common feature of Addison's disease,[29,56,173] also occurs frequently in presumed adrenal insufficiencies of minor degree, e.g., during convalescence from infections, and in hypopituitarism.

Restoration of hypoadrenal hypotensive blood pressure levels to normal is easily achieved by the administration of adrenal cortical hormones, whereby DCA proves more effective than other corticoids. If combined with an excess of sodium, DCA may raise the blood pressure to hypertensive levels.[130]

COMBINATIONS WITH RENAL MECHANISMS

As far as renal derangements are concerned, which either dominate the clinical picture or must be suspected as causally participating, even though inconspicuously, in a large number of patients with essential hypertension, a probably significant involvement of nephrogenic pressor

agents has been established.[159,170] This raises the question of whether or not neurogenic and hormonal factors can be integrated with renal changes producing hypertension.

Adrenal Cortical Overactivity: The possibility of a contributory role of adrenal cortical overactivity in the pathogenesis of some cases of renal hypertension may be inferred from the development of renal vascular lesions following experimental overdosage of DCA,[165,167] and from the frequent presence of renal disease in cases of primary clinical hyperadrenocorticism.[151]

The experimental syndrome of "post-DCA," "metacorticoid" or "self-sustained" hypertension[46,63,69] is, likewise, generally attributed to corticoid-induced irreversible renal vascular damage.[16,51]

Indications of participation of an adrenocortical factor in established renal hypertension[30] are of an indirect character. Corticoid-induced augmentation of plasma hypertensinogen,[73] and a prevention or diminution of experimental renal hypertension by adrenalectomy[130,199] suggest an adrenocortical element in the mechanism of renal hypertension. The presence of increased amounts of sodium in the vascular walls[145] and in the entire body[90] of animals with renal hypertension, as well as the blood pressure-lowering effect of sodium withdrawal in some of them,[44,71] appear to be consistent with this view.

Observations concerning an exaggerated pressor effect of renin[99] and of angiotonin[68b,69] in animals treated with DCA, and a weakened response to renin after adrenalectomy[20,45,153] are reminiscent of corticoid and cortical deficiency-induced alterations, respectively, of vascular sensitivity (see section on pressor effectiveness of catecholamines). It should be mentioned, however, that the diminished effect of renin was ascribed to a reduction of hypertensinogen (precursor) in the plasma, rather than to decreased vascular sensitivity.[20,153]

An accentuated pressor effectiveness of norepinephrine and epinephrine in rats with renal hypertension[110] is of ambiguous significance, as it may be due to either a real vascular hypersensitivity or merely an elevated baseline tonus[144] or to secondary hypertrophic thickening[1b, 39b] of the vessels. However, the finding of an increased vasoconstrictor action of norepinephrine on isolated vessels of rats with renal hypertension, and of its disappearance after adrenalectomy[102] favors the assumption of true vascular over-reactivity. In nephrectomized animals, the pressor effects of epinephrine,[80] hypertensin and renin[68b,80] have, likewise, been found increased.

No conclusive assay data regarding the degree of adrenal corticoid formation and excretion in renal hypertension are available. Thus, the attractive hypothesis of Friedman and Friedman[46] which attributes the features suggesting cortical overactivity to renal retention of normally excreted corticoids, is still in need of confirmation.

Neurogenic Neurohormonal Factors: Whereas the primary neurogenic mechanisms of hypertension are practically the only ones taken into consideration by the Pavlov-dominated Russian school of investigators,[169] even with regard to the manifestly renal forms, the significance of primary neurohormonal factors in the pathogenesis of renal hypertension has been treated rather casually in the Western hemisphere. Yet, the most unquestionably neurohormone-induced (even though not centrogenic) type of hypertension, that occurring in association with pheochromocytoma, offers valuable clues regarding the development of secondary renal disease under the influence of overactive adrenosympathetic catecholamines.

It is known that stimulation of the renal nerves,[85,156] as well as injected epinephrine and norepinephrine,[3,91,107,171] constrict the renal vessels, and that in cases of pheochromocytoma either temporary episodes of severe renal functional impairment ("paroxysmal nephropathy"[36]) or chronic but reversible or permanent renal lesions occur.

In addition there are forms of partially renal hypertension in which the participation of a neurogenic-neurohormonal pathogenic element may be tentatively concluded from a history of emotional tensions, hostilities and frustrations,[57,204] and from their response to interferences in the neurovegetative system, such as vasodepression under the influence of hyperventilation,[122] barbiturates, lumbar puncture and ganglionic blockade, and an exaggerated pressor reaction to breath-holding and cold stimuli.[130,159] These tests frequently yield positive results in patients with clinically manifest renal disease. Similar observations have been made in metacorticoid, presumably nephrogenic, hypertension.[64,65,175] Such indications of contributory neurogenic factors in the maintenance of chiefly nephrogenic blood pressure elevations may be attributable to reversible renal arteriolar constriction,[105,106] to the tendency of the carotid

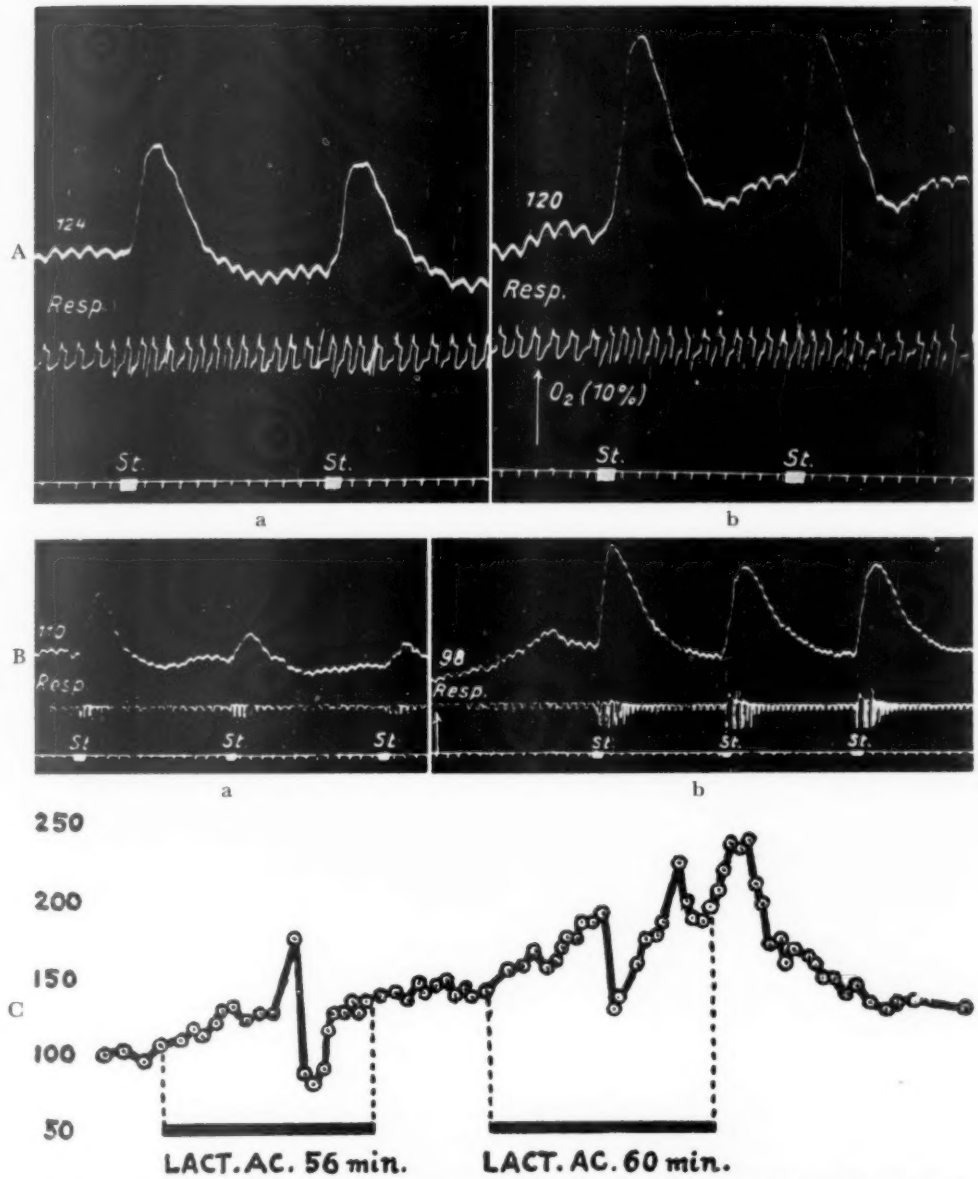

FIG. 11. Exaggerated excitability of vasoconstrictor centers of the brain stem by hypoxia and acidification with lactic acid. A, Pressor responses of the decerebrate cat to stimulation (St.) of the crural nerve. (a) under standard conditions; (b) during breathing of 10 per cent oxygen. B, the same; (a) under standard conditions; (b) during perfusion of the brain stem with addition of lactic acid. C, hypertensive effect of prolonged perfusion of the brain stem of the decerebrate cat with blood plus lactic acid (temporary falls due to manipulation of peripheral vessels). (From RAAB, W. Central vasomotor irritability; contribution to problem of essential hypertension. *Arch. Int. Med.*, 47: 727, 1931.)

sinus baroceptor mechanisms to reset at an augmented blood pressure level under the influence of renal hypertensive mechanisms,[83b,101] and to local vascular ischemic stimulation (arteriolar sclerosis) of the hypoxia- and acidity-sensitive cerebral vasoconstrictor centers[37,109,121,122,157,183] (Fig. 11).

In cases of advanced renal insufficiency, the catecholamine level of the blood is usually increased[97,127,139,206] (Fig. 8), presumably due to impaired elimination.[133] Part of the circulating extra catechols are probably derivatives of norepinephrine and epinephrine degradation. This may be manifested by a "false positive"

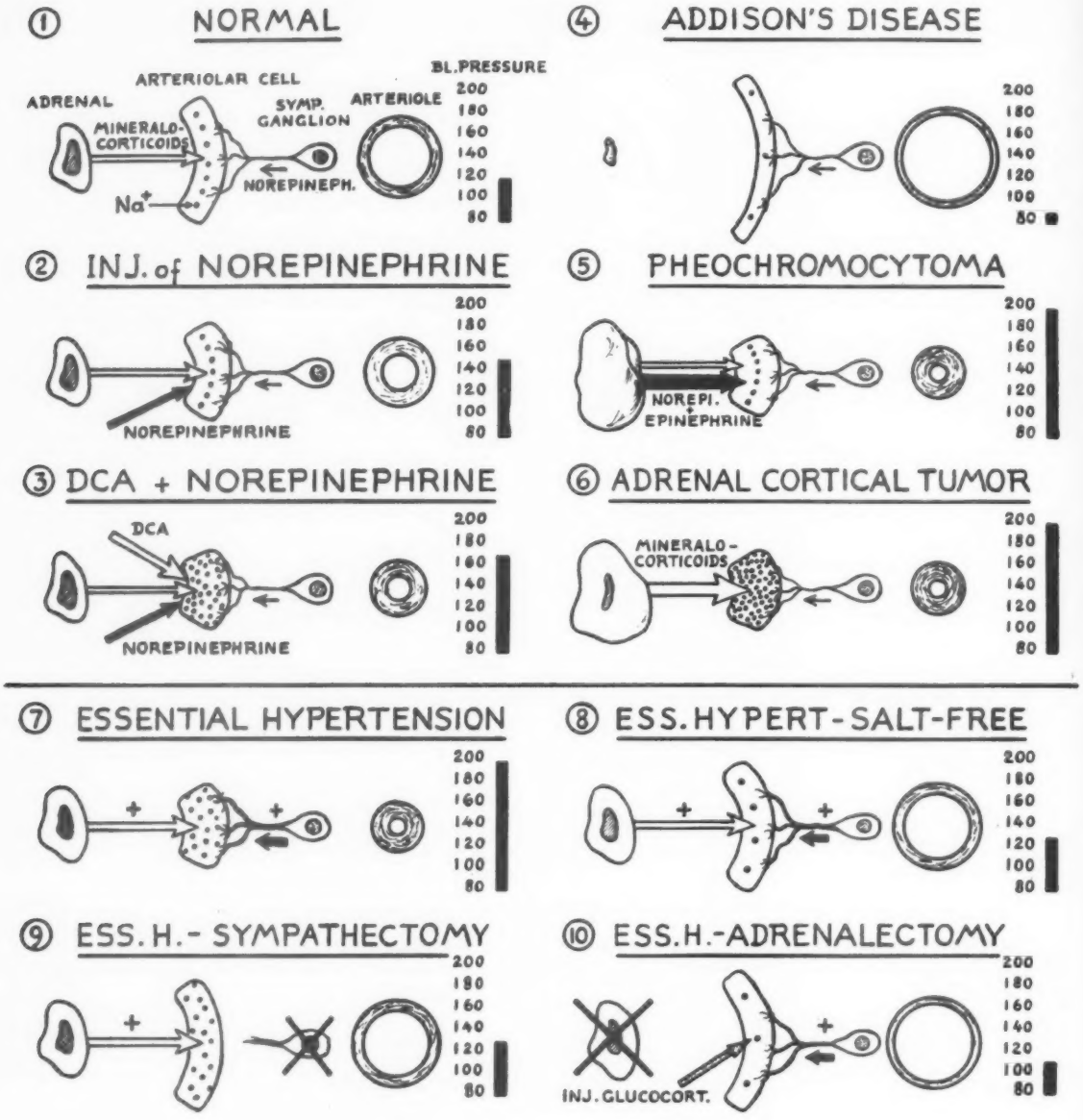

FIG. 12. Schematic representation of presumed integrated roles of sympathetic-neurohormonal, adrenal-cortical and sodium actions on arteriolar cell in determining blood pressure level. 1, mineralocorticoids hold normal amount of sodium (black dots) in cell, thus permitting normal reactivity to intrinsic sympathogenic norepinephrine (normal vascular tone).[50,129,130] 2,5, injected (2) and secreted (5) excess of norepinephrine constricts. 3,6, excess mineralocorticoids[189] (injected DCA, adrenal cortical tumor) augment intracellular sodium and thus potentiate constrictory effect of injected (3) or intrinsic (6) norepinephrine.[123,137,141] 4, lack of intracellular sodium, due to lack of mineralocorticoids, reduces reactivity to intrinsic norepinephrine.[130] 7, moderate increase of intrinsic norepinephrine (emotional, reflex, etc.) and/or mineralocorticoids (stress, etc.) causes exaggerated constriction (analogous to 2 and/or 3).[130] 8, dietary sodium restriction reduces intracellular sodium[186] and thus diminishes reactivity to intrinsic norepinephrine,[138] possibly in analogy to 4. 9, sympathectomy and ganglionic blockers withhold norepinephrine from vascular cells; reserpine diminishes vascular wall norepinephrine.[12] 10, adrenalectomy (with glucocorticoid substitution) decreases intracellular sodium and thus diminishes reactivity to intrinsic norepinephrine (analogous to 4). Not included in this scheme: Primary nephrogenic mechanisms, hypercatecholemia in excretory renal insufficiency,[127,139] serotonin, and other factors, such as potassium loss from vascular cells due to norepinephrine,[190] "water-logging"[144] and hypertrophy[39b] of contractile cells. (From: RAAB, W. *J. Mt. Sinai Hosp.*, 19: 233, 1952.[129])

Regitine® test for pheochromocytoma in patients with uremia.[130]

Therapeutic Implications

Generally speaking, therapeutic measures have been found to be effective in varying degrees if they made use of the following mechanisms, either singly or in suitable combinations (Fig. 12): (*1*) *decrease of catecholamine action on the vascular walls* by suppression of central nervous stimuli (psychotherapy, barbiturates, reserpine), by surgical or pharmacodynamic interruption of norepinephrine-discharging sympathetic pathways (sympathectomy, ganglionic blockade) and/or depletion of the vascular catecholamine stores (reserpine); (*2*) *decrease of body sodium* and, more specifically, *sodium depletion of the contractile vascular cells*, either by severe sodium restriction, administration of salt diuretics (chlorothiazide) or subtotal adrenalectomy.

Failure to achieve satisfactory results with these measures is believed to be due to the persistence of primary vasopressor renal mechanisms which are not directly affected by either (1) or (2).

Further elucidation of the mutual interactions between corticoids, electrolytes and catecholamines on the one hand, and renal vasopressor agents on the other, will undoubtedly contribute to the development of new and more potent methods for the treatment and prevention of arterial hypertension.

Summary

Corticoid-induced potentiation of catecholamine pressor reactions, and the constant presence of catecholamines in arterial walls have been demonstrated. It has been proposed that the degree of vasoconstrictor effectiveness of intrinsic vascular catecholamines "is determined by the intra-extracellular electrolyte concentration difference, which, in turn, is influenced by the adrenal mineralocorticoids by virtue of their specific ability to deposit sodium intracellularly."[129]

A considerable amount of evidence has accumulated in support of this concept. Pending availability of methods for direct measurement of vascular transmembrane cationic gradients *in vivo*, it constitutes a plausible explanation of the primarily neurohormonal hypertension in cases of pheochromocytoma and of the primarily hormonal hypertension of hyperadrenocorticism and toxemia of pregnancy. It is consistent with the lowering of the blood pressure after procedures which reduce catecholamines and/or corticoids. The question of how dietary sodium restriction and natriuresis affect the transmembrane cationic gradient is still in need of exploration.

Conditions in essential hypertension are complex due to the presumably frequent presence of nephrogenic pressor agents. However, here too, neural (catecholamine) and hormonal (corticoid) pathogenic elements are often discernible. Their abolition is believed to account for the therapeutic results of specific antiadrenergic treatments (sympathectomy, ganglionic blockade, reserpine), as well as of adrenalectomy, dietary sodium restriction, drug-induced natriuresis (chlorothiazide) and combinations of these.

Although prevailingly renal hypertension proves most refractory to such measures, it nevertheless permits clinical amelioration in a minority of cases in which neurohormonal-hormonal factors seem to coexist with renal mechanisms.

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Experiences with Coarctation of the Aorta*

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THE TERM coarctation of the aorta designates a significant luminal narrowing of an aortic segment. Commonly the stricture is located near the insertion of the ligamentum arteriosum. When it occurs at this level, the condition usually is manifested by evidences of impedance to the circulation distal to the obstruction. At the same time, in most cases there is hypertension of the upper extremities, overwork of the left ventricle and a tendency toward development of cerebrovascular accidents and heart failure. Indeed, coarctation is one of the most common causes of congestive heart failure in infancy and childhood.[1]

It is estimated that only 25 per cent of untreated patients reach the age of forty years. Reifenstein, Levine and Gross[2] have shown that prior to 1944 approximately 25 per cent of these patients died of subacute bacterial infection, 25 per cent from the sequelae of hypertension (heart failure, cerebrovascular accidents, etc.) and another 25 per cent from aortic rupture.

Following the successes of Crafoord[3] and Gross[4] in 1944 in the surgical treatment of this condition by excision of the narrowed area and direct end-to-end anastomosis of the two segments, the outlook for patients so treated has become excellent.

CLASSIFICATION

While the classification of Bonnet[5] still has many adherents, we are of the opinion that it is inadequate to embrace all of the several forms of coarctation of the aorta. Its primary basis is the division of these lesions into the "adult" form which is characterized by obliteration of the patent ductus arteriosus with extensive overdevelopment of a collateral arterial system, and the "infantile" form in which there is little collateral development and the lower aortic segment is supplied with venous blood from the pulmonary artery by way of a patent ductus arteriosus. Yet, the "infantile" form may be seen in adults and the "adult" form necessarily must occur first in infants. Furthermore, a patent ductus may be present in the "adult" form.

A more complete and yet simplified classification which has been presented previously[6] is the following:

Type I. Classically located coarctation with ligament (ductus arteriosus obliterated) (Fig. 1A). Over 98 per cent of clinical cases fall into this type and type IIA.

Type II. Classically located coarctation with shunt (Fig. 1B). (A) Ductus arteriosus present and patent to upper aortic segment with left-to-right shunt. (B) Ductus arteriosus present and patent to lower aortic segment with right-to-left shunt. These shunts should be expressed in liters per minute and may become reversed (which should then be so indicated in descriptions).

Type III. Coarctation of the aorta with hypoplasia (usually of the entire descending aorta) (Fig. 1C).

Type IV. Isthmus interruption (Fig. 1D). Etiologically and pathologically, this condition differs from true coarctation in that a segment of the aorta actually is absent. Physiologically, it is similar to type IIB coarctation, a patent ductus communicating the pulmonary artery with the lower segment which, therefore, is supplied with venous blood.

Type V. Coarctation occurring in an unusual location (Fig. 1E). (A) Ascending aorta (no recorded living case). (B) Aortic arch. (C) Descending aorta (including the abdominal portion). (D) Multiple sites of occurrence.

ETIOLOGY

Nearly all cases of coarctation are considered to be of congenital origin although Guastavino[7] has reported the successful correction of two abdominal aortic obstructive lesions of undoubted acquired origin. A summary of the various theories of embryologic origin may be found elsewhere.[8]

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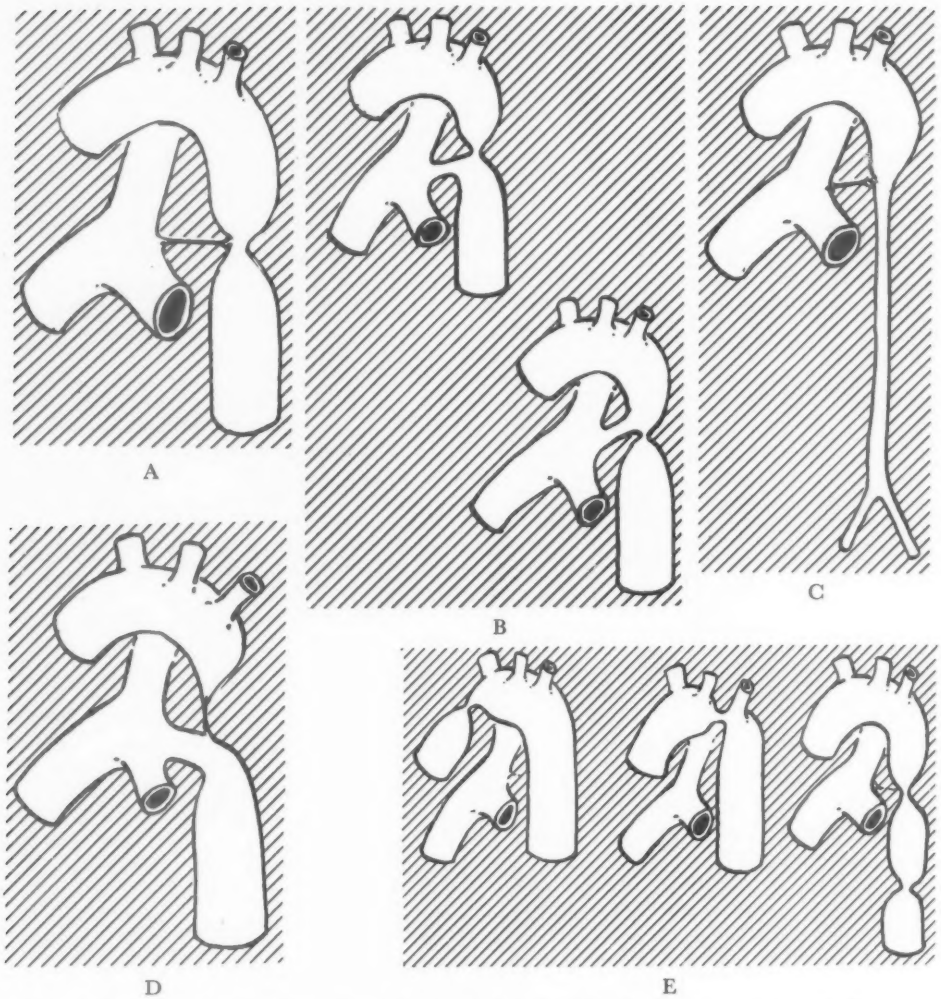

FIG. 1. Diagrams of the various types of congenital coarctation of the aorta. A, type I. B, type IIA (*lower*), type IIB (*upper*). C, type III. D, type IV. E, type V.

PATHOPHYSIOLOGY

In type I lesions hypertension usually exists in the portions of the body supplied by the upper segment of the aorta, while hypotension commonly exists in the lower portion. A vast collateral circulatory network is built up (probably mainly during fetal life). This is based primarily upon the tributaries of the two subclavian arteries. The fourth to the seventh intercostal arterial pairs are of fundamental importance in this collateral system since they communicate the distal segment of the aorta with the internal mammary artery. Other communications depend upon the scapular, lateral thoracic, transverse cervical and anterior spinal arteries.

In type IIA coarctations, a similar collateral system is developed. In addition, the usual auscultatory and hemodynamic evidences of a patent ductus arteriosus with a left-to-right shunt present themselves. Hypertension is prone to occur in the upper extremities, while arterial pulsations are weak or absent in the lower extremities.

In type IIB and type IV lesions, there is no overdevelopment of a collateral system, and the lower portion of the body is nourished with venous (pulmonary arterial) blood by way of the patent ductus arteriosus (right-to-left shunt). Hence, in the areas below the brim of the pelvis the patient manifests cyanosis. In these patients hypertension usually is not found in the upper extremities, and the pressure in the lower extremities is at pulmonary arterial levels.

Patients with type III lesions show collateral development and hypertension in the upper extremities. While the descending aorta may

sometimes be essentially atretic in this condition, those people who survive for a number of years usually have a diminutive or perhaps a minimally adequate aortic lumen.

Type V lesions are a non-homogenous group with protean (although appropriate) manifestations, dependent upon which individual variant is concerned.

Diagnosis

The most important ingredient in making a diagnosis of coarctation of the aorta is a high index of suspicion on the part of the examining physician. The recognition of hypertension of the upper extremities or of a systolic murmur over the precordium should be sufficient indication for an examination of the femoral arterial pulsations, inspection of the toenails for cyanosis, and measurement of the blood pressure in the lower as well as in the upper extremities. The presence of an abnormal pressure differential between the upper and lower extremities (normally, the systolic pressure in the legs is about 40 mm. Hg higher than that in the arms) is pathognomonic of coarctation of the aorta.

Surgical Considerations

Simple resection of the strictured segment between occluding clamps placed across the aortic continuity and reconstruction of the arterial passageway by direct end-to-end anastomosis of the cut aortic ends is the accepted treatment for type I lesions. Type IIA lesions may be treated in the same way, but patients with type IIB coarctation, having no effective collateral circulation, can tolerate complete interruption of blood flow through the distal portion of the aorta for only a short period. If the surgeon cannot complete the necessary manipulations and reestablish the circulatory continuity within twenty minutes, a high operative mortality and an even higher morbidity (paralysis of the lower extremities) will attend the use of this direct approach unless a temporary bypass shunt or hypothermia is employed. The lowering of the tissue metabolism by hypothermia permits a longer period of safe circulatory interruption.

In patients with type III lesions, resection and end-to-end anastomosis may be useful, provided that at least a minimally adequate lumen exists within the lower aortic segment. In more extreme instances, little will be gained by surgical intervention.

Type IV lesions are physiologically similar to type IIB lesions, and these patients should be operated upon under hypothermia or with the aid of a bypass shunt. In most instances, an arterial homograft or a plastic tube will be required to bridge the long arterial defect.

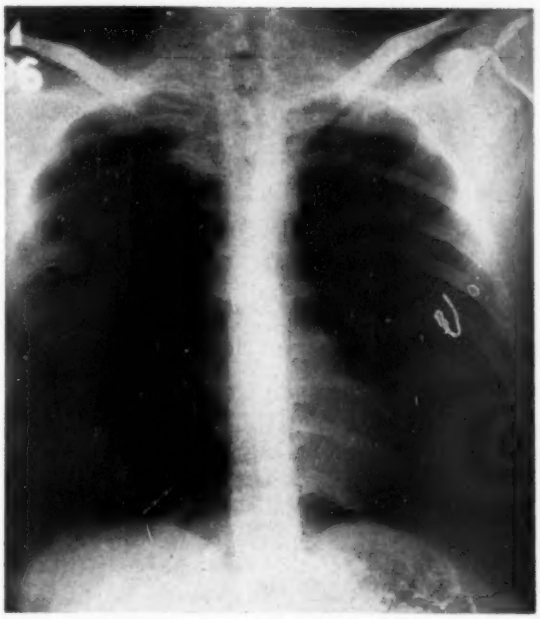

Fig. 2. Preoperative chest x-ray showing an intercostal artery aneurysm in the right upper chest, mistaken for a tumor at another institution where the correct diagnosis was made at thoracotomy. Note extensive bilateral notching of the rib.

Type V Coarctation: Therapeutically, patients with type V coarctation must be evaluated individually. In those patients with coarctation for whom resection and direct anastomosis would seem impossible or impracticable perhaps because of extreme length of the narrowed segment, several other alternatives remain open to the surgeon:

(1) The operative approach may be abandoned and the thorax closed. Actually this happened (at other clinics) to two of the patients included in the series to be reported here (Fig. 2). Neither had been helped and both subsequently survived completely corrective surgery.

(2) Simple closure of the aortic ends with no attempt at reconstruction. Historically, this procedure was the first recorded definitive surgical approach to a clinically recognized coarctation (with associated aneurysm).[9] Obviously, no physiologic benefit could be expected from such an operation.

(3) The use of the left subclavian artery to bridge the gap between the upper and the lower segments was first proposed by Blalock and

Park,[10] but Clagett[11] was the first to apply it clinically. Johnson and Kirby[12] have described several methods of enlarging a narrow proximal aortic segment, using the subclavian artery with or without a homograft.

(4) Division and anastomosis in continuity of the fusiform terminations of the segments may produce an adequate aortic lumen. The resulting passage may be smaller than desired, but Wiggers[13] has shown that aortic flow is adequate until the lumen is compromised by more than 60 per cent. Still another plastic procedure has been elaborated by Holman,[14] based upon the Z-plasty principle, to enlarge the aortic lumen at the site of the anastomosis.

(5) The insertion of a fresh or preserved arterial homograft has been recommended by Gross[15] to bridge the gap left by the removal of a long coarcted segment or by the inability to bring together the ends of an inelastic aorta. Isthmus interruption (type IV cases) amounts in effect to a very long site of coarctation. In some patients, an exaggeration of the usual poststenotic dilatation of the first portion of the distal segment may produce aneurysmal characteristics and, therefore, require the excision of a considerable length of the vessel so that end-to-end reconstruction becomes impossible. Creech[16] and Deterling[17] have recommended the use of prosthetic tubes of plastic fabric to connect the ends of widely separated aortic segments. The advantage of these artificial vessels is that they may be kept constantly available for use even in those clinics where facilities are not available for the preservation of vascular grafts.

INDICATIONS FOR SURGERY

It is now generally accepted that the mere anatomic existence of a type I or type IIA coarctation of physiologic severity (blood pressure level less in lower extremities than in upper) is sufficient indication for surgical correction. The only question devolves about the best age for intervention. Patients with types IIB, III, IV and V justify careful individual consideration. Perhaps it is better in them to consider any specific contraindications to surgery since the over-all operative mortality in uncomplicated cases of these types is higher than that which logically would be expected from intervention in patients with types I or IIA lesions.

CONTRAINDICATIONS TO SURGERY

The Presence of Acute or Subacute Bacterial Endocarditis: Surgery should not be undertaken until several months after complete antibiotic suppression of any such infection, except perhaps in a medically recalcitrant case, and then only as a rather desperate calculated risk.

The Presence of Congestive Heart Failure: In older patients this usually represents an irretrievably exhausted myocardium. In infants, there is much theoretical justification for immediate intervention to relieve the obstruction.[18] Nevertheless, some[19] have maintained that statistically there is an advantage even in these cases in deferment to a more opportune time.

Advanced Age: As our experience indicates and as other surgeons in this field have found,[20] older patients do not tolerate the necessary operative procedure as well as youngsters. With age, the arterial wall tends to become inelastic and fragile. Aneurysms of the lower aortic segment or of an intercostal artery are not infrequent. We consider age to be a relative contraindication with individual evaluation indicated. Certainly it does not comprise an absolute contraindication.

The Absence of Symptoms in Infants and Children: If the diagnosis of coarctation is established in one of these patients, follow-up may be continued to the age of six or eight years at which time operative intervention may be carried out under more nearly ideal conditions. Should difficulties arise at an earlier date due to the presence of the lesion, operation may be performed at once. The older child is a somewhat better operative risk, has larger and stronger tissues with which to work and may be more cooperative. Growth at the site of anastomosis has been proved experimentally and by clinical experience to occur, but may be insufficient in an infant.

The Presence of Associated Serious Congenital Anomalies: Hydrocephalus, mongolism and serious coexistent cardiovascular defects tend to negate the likelihood of worthwhile mental or physical salvage in these cases while greatly enhancing the operative risk.

Surgical Technic

The following is a description of the technic practiced at our Clinic. A long left posterolateral (parascapular) intercostal thoracic incision is used. The internal mammary artery should be spared because of the importance of its rich collateral anastomoses. The muscular arteries of the chest wall are dilated and upon division bleed furiously. While electrocoagulation is permissible for the control of smaller vessels, meticulous individual hemostasis with ligatures or sutures is mandatory for the larger ones. The incision is deepened and carried through the fourth

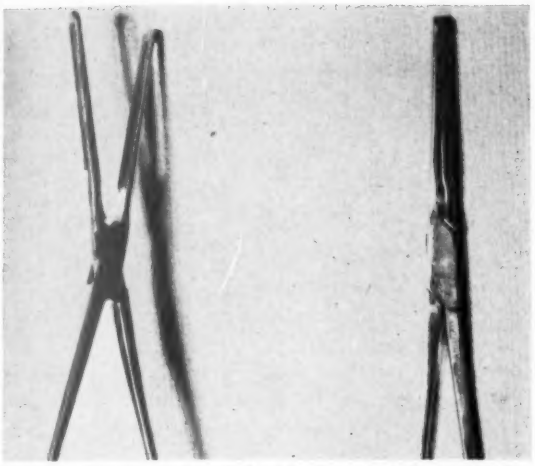

FIG. 3. Photographs of double fenestrated coarctation clamps. Only the upper portion of the clamps (blades) are shown.

intercostal space, and the ribs are spread apart in small increments in order to avoid fracture. Ordinarily, it is not necessary to divide the ribs posteriorly. The pleural covering over the lesion is incised longitudinally, and is dissected away from the aorta, from a point above the origin of the left subclavian artery to a distance of 6 cm. below the level of the coarctation.

The upper intercostal arteries are mobilized, taking care not to injure or interrupt any which come off that portion of the lower segment which is to be preserved. Sometimes one of these vessels will be found to be aneurysmal or extremely thin-walled (Fig. 2). Although it is our purpose to conserve as much as possible of the existing collateral blood supply to the lower segment, aneurysmal dilatation of an intercostal artery necessitates excision. Using the principle of preserving the entire existing collateral arterial bed whenever feasible, damage to the spinal cord is prevented during the course of the actual operative procedure, and maximal clinical improvement is afforded even in the event that a full normal sized aortic passageway should not be achieved.

The ligamentum arteriosum (or patent ductus arteriosus) is mobilized, the left recurrent laryngeal nerve being displaced medially. It should be understood that in a case of type IIB coarctation or of complete interruption of the isthmus (type IV) general bodily hypothermia should be induced since these patients will not have an adequate collateral circulation. If this has not been done in advance, the body now may be cooled by the recirculation of cold saline through the pleural cavity with a pump[21] to lower the temperature to 85°F. (29°C.) before interrupting the continuity of the lower segment with the pulmonary artery. The ligamentum (or ductus) is divided between clamps. If a lumen can be detected, the pulmonary end of the ductus is oversewn with continuous fine arterial silk. The aortic end remains clamped.

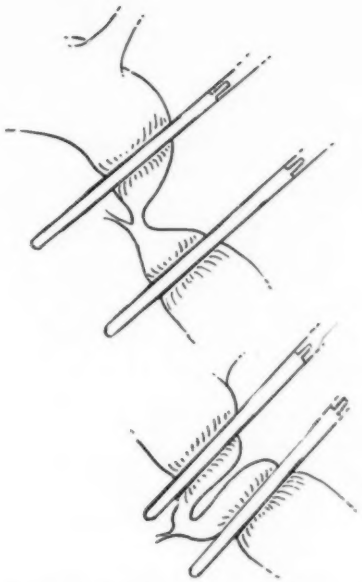

FIG. 4. Drawing showing approximation of aortic clamps prior to aortic division to establish feasibility of contemplated anastomosis subsequent to excision of the lesion.

The upper aortic segment is mobilized up to the subclavian origin. A tape placed beneath this portion of the aorta for traction aids significantly in freeing up the under surface of the coarcted area, the lower aortic segment and the right intercostal arteries.

Excision of Coarctated Segment: The coarcted area is dissected free, care being taken that no unexpected injury occurs to any vessel arising from its underside. It is then possible to appreciate fully the extent of narrowing and the length of the coarctation, as well as any existing poststenotic dilatation. Comparison of the respective calibers of the two segments and the slope of their fusiform ends permits selection of the optimal sites for aortic division and subsequent anastomosis.

The respective aortic segments are cross clamped with non-coupling toothed clamps at convenient levels above and below the selected sites of division. Because of their unusually secure gripping characteristics, we prefer to use the double fenestrated clamps which have been described elsewhere (Fig. 3). After application of the clamps, an attempt is made to bring the two sites of intended division into near or actual physical contact, thus establishing the possibility and feasibility of approximation of the aortic ends after division (Fig. 4). If any intercostal vessels arise proximal to the lower clamp, individual bulldog forceps are applied to them.

The coarcted segment is excised, care being taken to make the two aortic openings of comparable size and of equivalent obliquity (Fig. 5). The cut ends are approximated by drawing the clamps together, and the anastomosis is begun.

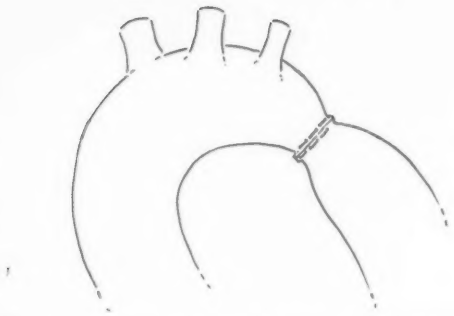

FIG. 5. Diagram of the cut aortic ends showing equal sizes and obliquity.

Anastomosis: In children, an all-interrupted technic may be employed, using No. 5-0 arterial silk. The repair having been accomplished with interrupted sutures, it is believed that the anastomotic site will grow normally. In adults, the posterior aspect of the aorta may be approximated with a continuous running suture of No. 4-0 or 5-0 silk, although some surgeons adhere to a mattress eversion type suture. The anterior aspect of the anastomosis may then be completed with interrupted simple sutures of fine silk (No. 5-0). However, a continuous technic is permissible in adults since no growth of the anastomosis is to be expected. Regardless of the exact technic of suture, the application of the posterior row of sutures may be facilitated by rotating the clamps medially, thus exposing the posterior aspect of the aorta. Dilute (1:1000) heparin solution is used to flush the open vascular ends from time to time, and to fill the aortic lumen just before tying down the final stitch.

The integrity of the anastomosis is tested by permitting the excluded portion of the aorta to become distended with blood. This may be done either by removing one of the bulldog clamps upon an intercostal artery or by releasing slightly the lower aortic (fenestrated) clamp.

If bleeding occurs between two sutures or through a suture hole, the clamp is reapplied and the disclosed leak is repaired with No. 5-0 arterial silk. When full vascular integrity has been established, the anastomosis is encircled with a gauze pad, and the lower clamp is removed. After the passage of a few minutes, during which time the anastomosis is constricted by digital pressure against the gauze, the upper clamp is loosened slightly to permit some blood from the aortic arch to traverse the anastomosis. The anesthetist is alerted to keep constant check upon the blood pressure in the upper extremities. If the patient's condition remains satisfactory, the upper clamp is released in small increments over a five-minute period, finally being removed. Should the blood pressure fall precipitously, the clamp is retightened for a time, and then more cautiously loosened. Usually there will be no bleeding from the anastomotic line or from a suture hole.

The mediastinal pleura is reconstructed over the site of anastomosis, leaving a gap for drainage at the caudal extremity of the pleural incision. The pleural cavity is inspected and, if found to be dry, the chest is closed, leaving a multi-windowed No. 24 French catheter inserted through an intercostal stab wound in place for postoperative underwater-seal drainage.

TABLE I
Age Incidence in our Series

Age in Years	No. of Patients
3–10	7
11–20	24
21–30	11
31–40	11
41–50	5
Total	58

CLINICAL MATERIAL

Our operative series consists of fifty-eight patients operated upon for coarctation of the aorta. They varied in age from three to forty-eight years (Table I). There were forty-three males and fifteen females. Two were Negroes; the remainder were of Caucasian origin.

The chief complaints presented by these patients are summarized in Table II. It is interesting to note that one-third of these patients consulted us because of the known presence of a heart murmur, while one-fourth were concerned about the previously recognized hypertension of the upper extremities. Only seven were seriously troubled with headache; only five had dyspnea. Precordial pain was present in four.

TABLE II
Chief Complaint on Admission

Complaint	No. of Patients	Percentage
Known presence of a heart murmur	18	31.0
High blood pressure	16	27.6
Headache	7	12.0
Exertional dyspnea	5	8.6
Precordial pain	4	6.9
Fatigability	3	5.1
Cold feet	1	1.8
Congestive heart failure	1	1.7
Syncope	1	1.8
Palpitation	1	1.7
Weakness in legs	1	1.8
Total	58	100.0

TABLE III
Roentgenographic Findings (Forty-Seven Cases Reviewed)

Finding	No. of Patients
Left ventricular hypertrophy	41
Scalloping of the ribs	36
No scalloping	11
Questionable scalloping	2
Left ventricle normal	5
Aneurysm of intercostal artery	1

NOTE: Aortograms were performed in thirty-four of the fifty-eight patients in our series.

Of the entire group, fifty-four patients presented with a heart murmur which did not disappear with exercise. Four patients had no murmur. Fifty-four patients (93 per cent) had an abnormally elevated blood pressure in the upper extremities at the time of admission. Only four patients (7 per cent) had a normal blood pressure in the upper extremities, and in each of these there was no perceptible blood pressure or detectable pulse in the lower extremities. All these patients had a basal systolic cardiac murmur. In other words, every patient in this series could have been diagnosed correctly in a physician's office without further ado by adherence to the previously mentioned diagnostic precept (hypertension of the upper extremities or systolic basal murmur).

LABORATORY STUDIES

An *electrocardiogram* was obtained for each patient in order to determine the condition of the myocardium prior to subjection to the strain of operation. The record showed no abnormalities in nineteen patients and revealed evidence of left ventricular hypertrophy, strain or damage in the remainder.

The *roentgenographic findings* are presented in Table III. It is interesting to note that "scalloping" of the lower margin of the ribs was recognized in thirty-six (64 per cent) of the patients in this series (Fig. 2). This finding usually is considered to be pathognomonic of the presence of coarctation of the aorta. However, Neuhauser[23] has shown that intercostal neuromas (neurofibromatosis), aneurysm of the intercostal arteries, long standing superior vena caval obstruction, and even tetralogy of Fallot may produce erosion or "notching" of the lower rib margins. This phenomenon usually does not become manifest before the age of ten years, and may not be seen in older patients. The youngest patient in our series who showed "notching" was nine years of age. Neuhauser has observed it in a nineteen month old baby.

Formerly *aortography* was employed in every patient. Today, we use it only when there is some reason to suspect that the pathologic pattern may not fit within the type I classification. In one case, the distal aorta was opacified in order to rule out the possibility of multiple sites of coarctation.

TABLE IV
Operative Findings in Fifty-Eight Patients

Finding	No. of Patients
Ligamentum arteriosum (type II)	50
Patent ductus arteriosus (type IIA)	5
Patent ductus arteriosus (type IIB)	1
Hypoplastic descending aorta (type III)	2

OPERATIVE FINDINGS AND PROCEDURES

Our operative findings are presented in Table IV. In no case did we find an arterial aneurysm of the aorta even though the average age in the series was above twenty-two years, nor did we encounter any of the rarer types of coarctation. Only two patients presented hypoplasia of the descending aorta (type III). Fifty-two of the patients were found to have a ligamentum arteriosum (type I). Only six patients had a patent ductus arteriosus; five were type IIA, and one was type IIB.

Resection of the stricture and end-to-end anastomosis of the cut ends was carried out in all but two patients. In both of these, the distal end of the subclavian artery was turned down

FIG. 6. Drawing showing subclavian artery being anastomosed to distal aorta, bypassing coarctation in an oblique end-to-side technic.

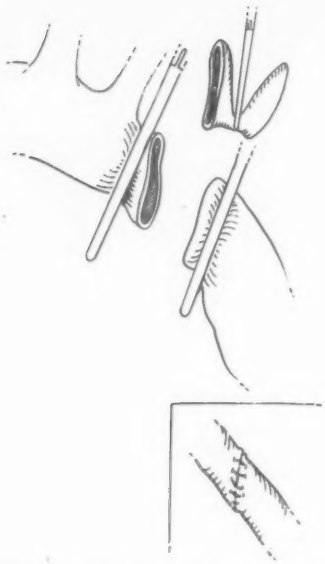

FIG. 7. Drawing showing fusiform aortic anastomosis with lumen smaller than desired.

and sutured to the lower aortic segment. In one of these two, the stricture was first resected, the upper end being closed as recommended by Clagett.[11] In the other, the stricture was left intact, the distal end of the subclavian artery being anastomosed to the distal aorta in an oblique end-to-side technic (Fig. 6).

In one patient, the anastomosis was performed in the fusiform portions of the two aortic ends so that an aortic lumen smaller than desired was finally provided (Fig. 7). This patient had an aneurysm of the third right intercostal artery resected simultaneously (Fig. 2). An excellent clinical result was obtained (blood pressure of upper extremities was reduced from 180/90 to 126/88 mm. Hg). In retrospect, a better aortic passageway might have been provided in all three of these patients by the use of homografts. However, each of them has exhibited a good clinical result.

One patient, an eleven year old boy, had an extreme degree of hypoplasia of the aorta below the level of the coarctation. The lower aortic lumen was so small that there was considerable doubt in the mind of the surgeon whether or not improvement in his circulation had been provided by the operation. However, the blood pressure in the lower extremities averaged 120/0 mm. Hg before surgery and 170/110 mm. Hg afterward.

Immediate Surgical Mortality: It is important to note that we did not deny operation to any patient, not even those with known complications which may have increased the operative risk. All were considered to have received some benefit from surgery.

The hospital mortality in this series of cases was one (1.7 per cent). A hemothorax and a staphylococcic empyema developed in this patient, and his anastomosis finally disrupted on the forty-first postoperative day. This low mortality rate contrasts with an over-all operative mortality of 8.6 per cent in 1,601 patients operated upon by thirty-six surgeons comprising the Advisory Committee of the American College of Chest Physicians.[25] The postoperative period of hospitalization in our series, including all complications, averaged 13.8 days.

Late Deaths: Four patients have died since surgery. In each instance death was due to some complicating factor unrelated to the operation or the operative result achieved. One patient had congenital aortic insufficiency with a minor degree of aortic stenosis. He succumbed to the effects of the insufficiency two years after successful excision of the coarctation. Another patient with known coexistent aortic stenosis was performing strenuous labor (against the advice of his physician) when he suddenly died, nine months after the operation for coarctation. An autopsy indicated that he probably died of acute coronary insufficiency. A third patient died more than three years after excision of the coarctation and anastomosis. This patient had undergone an aortic commissurotomy for stenosis performed four months prior to his death. He had had a complicated (second) postoperative course. While at home, an abscess of the right side of the mediastinum developed which eroded a major vessel producing a massive hemorrhage that caused death. The fourth late death occurred in a child who had been treated elsewhere by irradiation for a Wilms tumor prior to undergoing operation for coarctation. Postoperatively, his diastolic pressure was normal (240/80 mm. Hg in the left arm), with a blood pressure of 170/110 mm. Hg in the legs. Fourteen months after surgery he had a massive cerebral hemorrhage and died. A renal factor has been suggested in patients who have had an adequate technical operative result, but who have experienced little or no lowering of their elevated blood pressure.[24]

RESULTS OF SURGERY

FOLLOW-UP

Of the fifty-eight patients in this series, a follow-up has been possible in all patients who sur-

vived surgery. However, in two, residence in a foreign country rendered it necessary to accept a second-hand medical report. The longest follow-up was eight years and ten months; the shortest was six months.

BLOOD PRESSURES

It was possible to obtain a recent direct follow-up on the fifty-one surviving patients. Forty-five of these (88 per cent) may be classified as having an excellent result. Each of these has been relieved of his symptoms, and the blood pressure of the upper extremities is within normal range for the age. All have a normal blood pressure in the legs, or, if it has not been recorded, there are excellent pulsations in the lower extremities which were non-existent before surgery.

The remaining six patients have normal blood pressure in the lower extremities, none having been detectable prior to the operative intervention. Four of these patients have a diastolic pressure of 90 mm. Hg or less in the arms, while the other two have recorded diastolic pressures of 92 and 106 mm. Hg, respectively. Their average systolic (arm) blood pressures range from 150 to 178 mm. Hg, respectively. Their ages range from twenty-two to forty-two years, being older than the mean age of twenty-two years. The patient with the highest remaining blood pressure was forty-two years old at the time of surgery (preoperative blood pressure 240/134 mm. Hg, postoperative blood pressure 178/92 mm. Hg). This small proportion of the over-all series suggests that the older patient is not as likely to receive as much reduction in blood pressure of his upper extremities as is the person who undergoes operation at a younger age. In summary, each of these six patients may be said to have had a moderately satisfactory result since each has been relieved of his subjective complaints, has had appreciable reduction in blood pressure levels, and presumably, is no longer subject to the full natural ravages of the disease.

The two patients who have persistent elevation of the diastolic (upper extremity) blood pressure possibly may have an element of essential hypertension in addition to the basic disease. The diastolic hypertension had been present for twenty-two and forty years, respectively, prior to surgery.

COMPLICATIONS OF SURGERY

Of the complications occurring in the hospital pleural effusion was most common, thoracentesis being required in sixteen patients (Table V). Two patients required postoperative bronchoscopy for retained secretions, and two required closed thoracotomy for recurrent pneumothorax after the chest tube was removed. Two children suffered necrotizing arteries of mesenteric vessels on the seventh and eleventh day after operation.[26] Presumably this complication is due to the inability of these vessels to tolerate the sudden increase in blood pressure and flow afforded by the operation, and, hence, may be unavoidable in some individuals.[27] Another patient suffered from prolonged abdominal distention of a transient nature. One patient has had persistent hoarseness apparently due to injury of the left recurrent laryngeal nerve. Discharge from the hospital was delayed for several days in one case because of a minor wound infection. Two patients suffered postoperative cerebrovascular accidents. In both the signs had cleared up without significant residue by the time of discharge. These patients were thirty-eight and forty-eight years of age, respectively, the latter being the oldest in the series. The former was the patient who subsequently died (nine months later) from aortic stenosis.

TABLE V
Complications of Surgery

Complication	No. of Patients
Pleural effusion requiring one thoracentesis*	10
More than one thoracentesis	6
Retained secretions—bronchoscopy	2
Pneumothorax—closed thoracotomy	2
Cerebral vascular accident	2
Wound infection	1
Hoarseness	1
Abdominal distention	1
Necrotizing arteritis—bowel resection	2
Hemothorax, empyema, disruption of aorta	1
Total	28

* With a large house staff and many people involved in the care of our patients, we leave as little to chance as possible. It is a basic rule in our Clinic that if any fluid at all is seen on any postoperative chest x-ray, a thoracentesis is performed.

COMMENTS

Combined Coarctation and Aortic Stenosis: Although the etiology of this crippling and frequently fatal disease is unknown, modern surgical treatment has been developed to the status

of a finished product. When there is a significant gradient across the aortic valve (greater than 30 mm. Hg), it is advised that the surgeon follow the operation for coarctation with relief of the stenotic aortic valve. However, since these deformities of the valve are congenital and not acquired, planned open heart surgery on the valve with the aid of hypothermia or a heart-lung machine would seem to be preferable. Our total experience with this combination of lesions (five) is the subject of a detailed study in a forthcoming report.[28] Three of the patients in this reported series underwent both operations at the same time (closed transventricular dilatation of the aortic valve and resection of the coarctation). Each is living and well, with a good clinical result.

Optimal Age for Surgery: There are several reasons why patients with coarctation of the aorta should undergo surgery at an early age. It is a generally accepted fact that children and young adults withstand surgery much better than the mature adult. The soft elastic aorta of youth provides the surgeon an ideal tissue with which to work. In our experience, those in the younger age group develop fewer complications. With two exceptions, they have been of a less serious nature than those of the older patients. Furthermore, younger people may expect a better result from the viewpoint of the fall in blood pressure of the upper extremities than those past twenty-five or thirty years of age. Since coarctation is chiefly a disease afflicting males, who are the usual breadwinners, the attending physician should recommend corrective surgery before a patient attains the greater responsibilities of life. From the surgical standpoint, the age range of six to eighteen years is ideal.

Surgical Technics: The operative technic practiced in our Clinic is designed to save operative time and blood loss. Nearly all of the collateral circulation is left undisturbed both during and after the operation. Hence, should the provided anastomotic lumen not be ideally large, it will at least represent a clear-cut net gain. The recommended degree of mobilization of the aorta has proved adequate for every eventuality which has arisen, but our dissection is limited to the immediate area of the lesion and a few centimeters on either side.

Of the various possibilities for reconstruction of a long coarcted segment, we favor either the use of a prosthetic graft or a plastic revision of the divided ends. Grafts were used in fifty-six (4 per cent) of 1,405 patients operated upon by members of the Advisory Committee of the American College of Chest Physicians up to 1956,[25] yet personal preference may have accounted for many of these. One surgeon used grafts in fifteen of his total series of twenty-two patients. The employment of the subclavian artery as a bridge for a long stricture is not very satisfactory in several respects. First, it needlessly sacrifices a perfectly good artery although no harm usually comes of it. Rarely, the vessel chosen might unknowingly be an anomalous right common carotid, section of which would leave the patient with brain damage and perhaps a complete left hemiplegia. The size of the lumen of the new blood conduit thus created might not be as large as that obtainable by the more favored methods. In one of our patients, this technic produced a satisfactory fall in the blood pressure in the right upper extremity (none obtainable in the left upper extremity), but the blood pressure in the legs has never been greater than that in the arms. This indicates that there remains some narrowing of the lumen at the site of anastomosis. In the other patient, a good clinical response has been obtained.

Indications for Opacification Technics: It is generally agreed that the angiogram or aortogram will not give an accurate impression of the condition of the distal segment unless performed in a retrograde manner. Yet, this is the information which is most desired. In doubtful cases the possibility of being forewarned regarding impending difficulties before the time of operation may justify the preoperative aortogram. Having a ready supply of prosthetic grafts as an additional source of security, we prefer not to carry out these additional diagnostic studies. Thoracotomy carries relatively little risk, perhaps less than that entailed in major investigations such as aortography. It will reveal information of more practical value.

Summary and Conclusions

Every practicing physician should have a high index of suspicion regarding the possibility of existence of coarctation of the aorta when confronted with a patient who presents with a systolic murmur and/or systemic hypertension. The diagnosis usually can be made accurately by clinical examination in the physician's office. The anomaly is surgically curable with an acceptable operative mortality and a high likelihood of a good clinical and physiologic result if corrected early.

A new system of classification for coarctations of the aorta has been developed and presented.

We have presented our experience with fifty-eight cases of coarctation of the aorta operated upon over a period of eight years and ten months. There was one operative (hospital) death in the series (mortality 1.7 per cent).

Certain aspects of our surgical technic permit us to perform rapid, safe and adequate surgery; these have been emphasized. The incidence of grafting was less than commonly practiced.

In five patients in this series, both aortic stenosis and coarctation of the aorta were found. In three patients, the coarcted segment was removed and anastomosis performed, followed by transventricular aortic dilatation. These have done well. The other two patients had excision of the coarcted area and anastomosis alone. Both of them subsequently died, one as a result of the valvular stenosis, the other due to complication of the required secondary surgery.

The rate of cure by operation for hypertension due to coarctation of the aorta is probably higher than for hypertension caused by any other condition. In 88 per cent of the patients in the series there was an immediate lowering of the blood pressure in the arms following operation and this has been maintained postoperatively. All of the patients followed up have excellent pulsations and/or normal blood pressures in the lower extremities.

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Report on Therapy

Diuretic Therapy in Syndromes Associated with Sodium and Water Retention*

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THE DISCOVERY by Vogl that the organic mercurial merbaphen (Novasurol®) produced diuresis initiated extensive studies on the effects of such compounds that have continued up to the present time. Until recently, diuretic therapy centered largely around mercurial compounds. Numerous non-mercurial diuretics for oral administration have now appeared. The carbonic anhydrase inhibitors and chlorothiazide, a compound with minimum carbonic anhydrase inhibitory effects, are outstanding examples. These agents appear to be indicated in the treatment of many diseases in which the kidneys fail to excrete adequate amounts of salt and water resulting in a wide variety of symptoms. The purpose of this paper is to review the pharmacodynamics and clinical use of these compounds.

PHARMACOLOGY OF MERCURIAL DIURETICS

Renal Function Studies: A substantial number of observations have been made on the effects of mercurial diuretics on renal functions. Except for a depression of renal tubular reabsorption of sodium chloride and water, no consistent change has been observed to occur.[1] This is true of normal subjects or patients with edema and experimental animals. It is generally assumed that specific transport systems are present in the cells of the renal tubule for the reabsorption and secretion of different ions and compounds present in the glomerular filtrate and the blood.[2–5] The composition of the urine before and during mercurial diuresis indicates a highly selective inhibitory action on only a few of these transport mechanisms.[6–8] There are proponents of the view that the primary effect is on chloride reabsorption while others favor the view that the primary effect is on sodium reabsorption. Definitive conclusions cannot be drawn since even though there is frequently a greater relative increase in the rate of chloride excretion, this could indicate an increased rate of excretion of cations other than sodium. Increased rate of water excretion usually follows increase in sodium and chloride excretion.

During mercurial diuresis the glomerular filtration rate may rise, fall or show no change. Changes in renal plasma flow show a similar inconsistency. One must conclude from these observations that changes in glomerular filtration rate or renal plasma flow are not involved in the diuretic effect of these agents. The effect of mercurial diuresis on potassium excretion is variable. Unless there is a massive diuresis, potassium excretion is not increased significantly (Fig. 1).[9] No serious disturbances of potassium metabolism occur with the usual clinical use of mercurial diuretics.

Many of the mercurial diuretics currently used are compounds formed by the reaction of theophylline with an organic mercurial. The result of such a reaction is to form a more stable, less toxic and more rapidly absorbed compound. After intramuscular administration of compounds of this type [for example, meralluride (Mercuhydrin®)] absorption is virtually complete. The amount of theophylline present in a therapeutic dose of a mercurial (98 mg.) is too small to exert any diuretic effect except by improving the rate of absorption of the mercurial.

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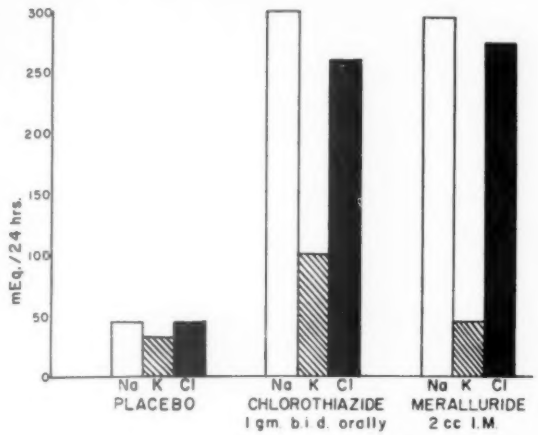

FIG. 1. *A comparison of the effect of placebo, chlorothiazide and meralluride on urinary electrolyte excretion.* When meralluride was administered parenterally, the primary effect was an increase in sodium and chloride excretion with a minimal effect on potassium excretion. When chlorothiazide was administered the primary effect was also on sodium and chloride excretion but there was also a significant increase in potassium excretion.

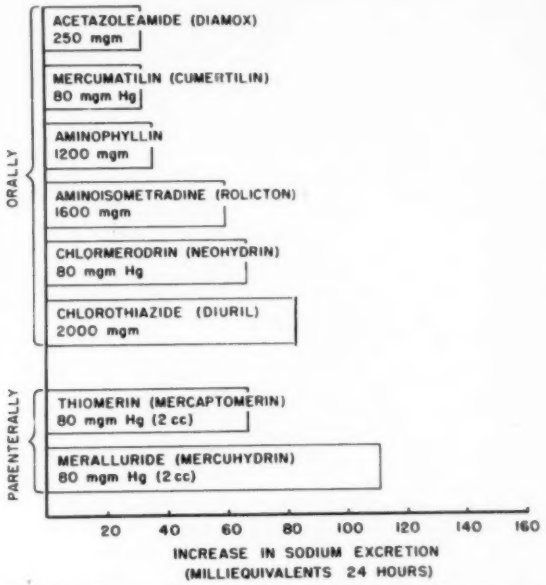

FIG. 2. *Comparative potency of various oral and parenteral diuretic agents.* Chlorothiazide administered orally was of the same order of potency as meralluride administered parenterally. Both of these agents were more potent than acetazolamide and chlormerodrin given orally and mercaptomerin given parenterally.

Mercaptomerin: A different type of compound was introduced more recently. The compound is known as mercaptomerin sodium (Thiomerin® sodium). In this compound, the theophylline of mercurophylline sodium has been replaced by sodium thioglycolate. This mercurial was studied after observations indicated that glutathione and cysteine reduce the cardiac toxicity of mercurials without influencing the diuretic effect. After intramuscular or subcutaneous injection the rate of absorption of mercaptomerin is of the same order as the aforementioned compounds, but the potency is not as great (Fig. 2). This compound is administered extensively by the subcutaneous route because of the low incidence of local reactions and pain at the injection site.

Parenteral Administration: The rate of excretion of mercury after subcutaneous, intramuscular and intravenous administration of meralluride is quite similar in patients with minimal edema. This indicates that the rates of absorption from both subcutaneous and intramuscular sites are very rapid, i.e., up to 90 per cent within twenty-four hours. The increase in sodium excretion parallels the excretion of the mercurial. In patients with severe heart failure, the urinary excretion of mercurials may be delayed somewhat following intramuscular or subcutaneous injection due to the poor circulation (Fig. 3). Unless absorption is delayed, 30 per cent or more of a therapeutic dose of a mercurial given parenterally is usually excreted in less than six hours.

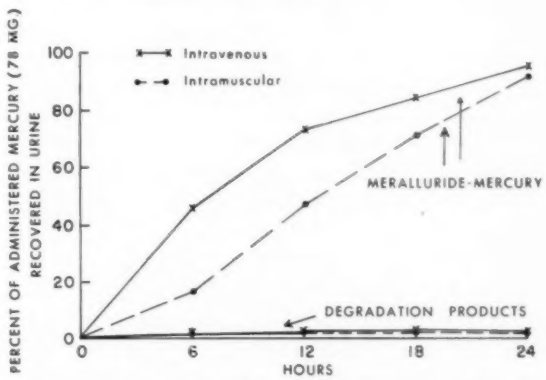

FIG. 3. *Comparison of excretion rate of meralluride (Mercuhydrin) following the intravenous and intramuscular routes of administration,* in a patient with edema and heart failure. About 70 per cent of the drug was excreted within twelve hours following administration by the intravenous route. The urinary excretion rate of meralluride was delayed following the intramuscular route of administration due apparently to a decrease in the rate of absorption from the injection site. (From: Moyer, J. H., Seibert, R. A. and Handley, C. A. *Circulation Res.*, 5: 493, 1957.)

Oral Mercurials: Oral therapy with mercurial diuretics was unsatisfactory until the recent introduction of chlormerodrin (Neohydrin®). Since absorption of mercurial diuretics from the intestinal tract was so limited, the amount of

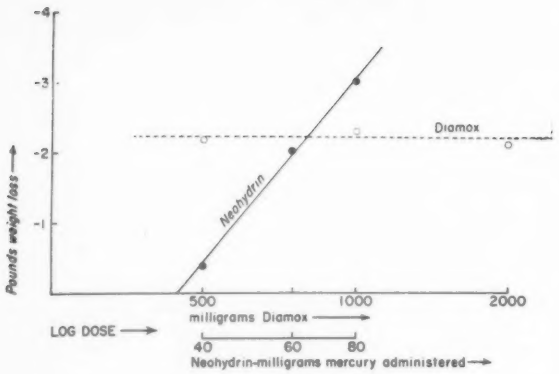

FIG. 4. *Dose response curve to chlormerodrin (Neohydrin) and acetazolamide (Diamox) using weight loss for comparison.* When the dose of acetazolamide was increased from 250 mg. to 2,000 mg. there was no increase in the response. However, when the dose of chlormerodrin was increased progressively, there was an increase in the degree of response. The minimal effective dose appeared to be approximately four tablets (equivalent to 40 mg. Hg). When the dose was increased to six tablets the response was equivalent to 250 mg. of acetazolamide and when the dose of chlormerodrin was increased to eight tablets the response exceeded the response to acetazolamide by a significant degree. (From: Moyer, J. H., McConn, R. G., Seibert, R. A., Dennis, E. W. and Hughes, W. *J. Chronic Dis.*, 2: 670, 1955.)

mercury that could be removed from the urine after oral administration of previously available mercurials was less than 3 per cent of the dose administered. This necessitated the use of large doses that frequently caused gastrointestinal distress. Not only is chlormerodrin better absorbed from the intestinal tract (up to 15 per cent), but it is also several times more potent than other currently employed mercurials.

It is essential that an adequate dose of this compound (four tablets or more per day which is equivalent to 40 mg. Hg) be administered if an effective diuretic response is to be obtained (Fig. 4). Increasing the dose above this amount increases the diuretic response progressively. An attribute of note with this compound, as with all organomercurials, is that daily administration results in persistent diuresis and natriuresis.

Pharmacology of Cytosine and Xanthine Diuretics

Xanthine derivatives, such as aminophylline and various salts of theobromine, have long been familiar adjuncts in cardiac therapy. These compounds are derivatives of purine which is found in nucleic acid. Despite much lower diuretic potency than other agents, the xanthines are still extensively tried in edematous states. This is probably a reflection of the absence of serious untoward reactions from these compounds and the unavailability of effective oral diuretics until comparatively recently.

Aminometradine (Mictine®) and aminoisometradine (Rolicton®) are recently introduced compounds proposed for use as oral diuretics. These compounds are derivatives of the pyrimidine base cytosine which also occurs in nucleic acid.

Aminophylline, aminoisometradine and aminometradine have similar effects on renal transport mechanisms for various electrolytes. All three cause an increase in excretion rate of sodium and chloride, slight inhibition of ammonia and phosphate without consistent changes in potassium and bicarbonate excretion. The increase in water excretion is probably secondary to the increase in sodium excretion. The maximum effects of intravenously administered aminophylline occur acutely within two hours.[10,11] Aminoisometradine and aminometradine exhibit their maximum effects within six to twelve hours after oral administration.

Pharmacology of Carbonic Anhydrase Inhibitors

Early in the use of sulfanilamide, it was noted that the drug produced a consistent reduction of plasma bicarbonate. Preceding this effect, the urine was observed to become alkaline as a result of increased bicarbonate excretion.[12,13] The discovery that sulfanilamide is an inhibitor of carbonic anhydrase[14] and the demonstration of a high concentration of this enzyme in the kidney[15] provided a basis for the mechanism of action of the drug. Carbonic anhydrase is a zinc-containing enzyme that catalyzes the reversible reaction:[16–18]

$$H_2O + CO_2 \rightleftharpoons H_2CO_3$$

These reactions occur in the absence of the enzyme, but the presence of carbonic anhydrase greatly accelerates the rates.

Compounds have been prepared with several hundred times the activity of sulfanilamide.[18] Among these, acetazolamide (Diamox®) and ethoxzolamide (Cardrase®) are the ones in current use as diuretics.

Renal Mechanisms for Maintaining Acid-Base Balance: The diuretic action of acetazolamide is intimately related to the mechanisms for maintaining acid-base balance and particularly to the important role of the kidney in this process.

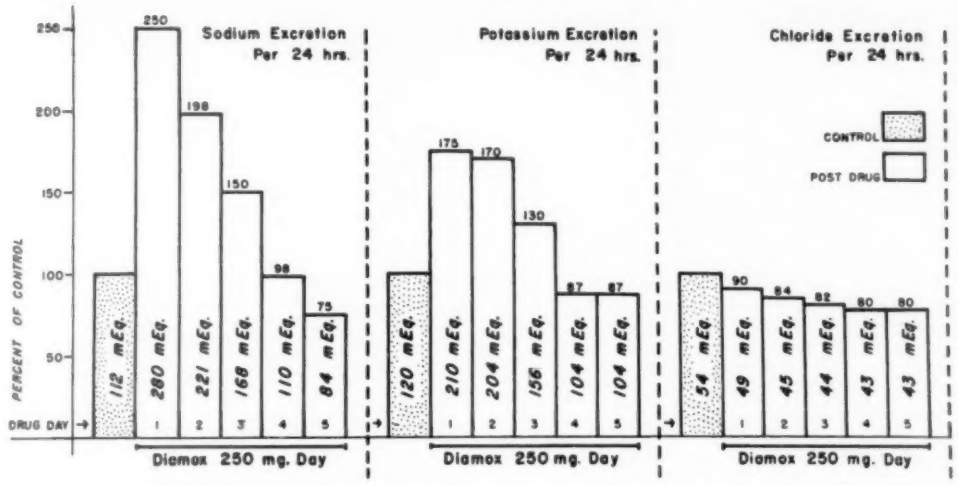

FIG. 5. *The electrolyte excretion response to acetazolamide with continuous daily administration.* The greatest increase in sodium excretion occurred within the first twenty-four hours. This response dropped off rather rapidly with daily administration so that by the end of the third day, the patient no longer obtained a natriuretic response to the drug.

Renal mechanisms contributing to acid-base balance are largely concerned with conservation of base and carbonic anhydrase is of prime importance in all these mechanisms. The following renal processes are fundamental for understanding the effects of carbonic anhydrase inhibitors on the kidney. The CO_2 produced metabolically in the cells of the renal tubule is immediately converted to carbonic acid by the enzyme carbonic anhydrase. Urine is acidified by the secretion of H^+ derived from carbonic acid formed in the tubule cells in exchange for Na^+ in the tubule lumen.[19,20]

The exchange of these ions normally conserves base in several ways. First, there is virtually complete reabsorption of sodium bicarbonate presented to the tubules in the glomerular filtrate. Reabsorbed Na^+ combines with bicarbonate in the tubular cells and is returned to the blood. The carbonic acid formed by the reaction of H^+ with bicarbonate in the tubular fluid is converted to H_2O plus CO_2 and the latter is returned to the blood by diffusion. Second, even after all the bicarbonate is reabsorbed from the tubular fluid, the exchange of H^+ for Na^+ continues to conserve base by other mechanisms. Secreted H^+ converts Na_2HPO_4 from the glomerular filtrate to NaH_2PO_4. This furnishes additional Na^+ for the exchange process and the exchanged Na^+ is again returned to the blood as $NaHCO_3$. Third, in the absence of both $NaHCO_3$ and Na_2HPO_4 in the tubular fluid H^+ and Na^+ exchange would be self-limiting because of an unfavorable H^+ gradient between the tubular cell and the lumen fluid if it were not for formation of ammonia, an additional function of tubular cells. The exchange of H^+ for Na^+ from NaCl would result in the formation of a strong acid. As the tubular fluid becomes acid, the tubular cells respond by synthesizing NH_3. The ammonia diffuses into the tubular fluid where it immediately reacts with H^+ to form NH_4^+.[21] Ammonia formation thus permits H^+ and Na^+ exchange to continue. These several processes are responsible for returning most of the Na^+ from the glomerular filtrate to the extracellular fluid.

Renal Effects of Carbonic Anhydrase Inhibitors: The administration of sufficient ethoxzolamide or acetazolamide to inhibit renal carbonic anhydrase exerts drastic effects on these basic mechanisms. The decreased rate of carbonic acid formation in the cells of the renal tubules greatly reduces the rate of H^+ and Na^+ exchange. Qualitatively uniform results have been observed in all mammals studied. The urine rapidly becomes alkaline and there is a marked increase in the rate of excretion of sodium, potassium and bicarbonate, and a decrease of titratable acid and ammonia.[22] With the exception of the increase in potassium excretion, all these changes are explained by the suppression of H^+ and Na^+ exchange. Potassium and H^+ are believed to be secreted by the same mechanism. Therefore, with decreased H^+ formation, the competition of the two ions for the transport mechanism is removed and more potassium is excreted.[23] The stimulus for am-

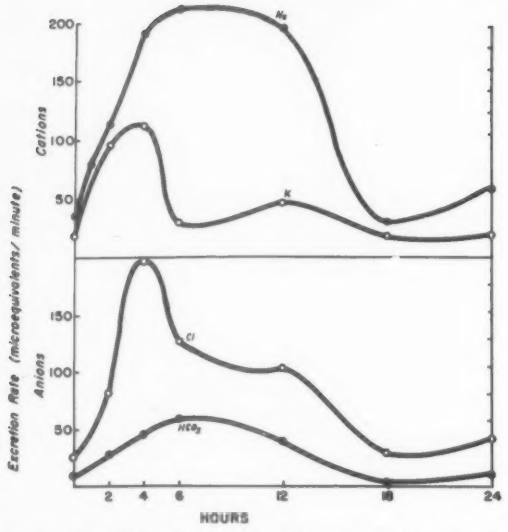

FIG. 6. *The effect of chlorothiazide on electrolyte excretion.* The maximum response was observed during the first six hours and the drug continued to be effective for twelve hours, returning to control levels by about the eighteenth hour. The primary effect was to increase sodium and chloride excretion with a lesser effect on potassium and bicarbonate excretion.

monia formation is an acid urine. Increased output of urine results from a larger solute excretion. Excretion of chloride and phosphate is not significantly changed.

Clinical Limitations: When therapeutic doses are administered, there are no significant changes in glomerular filtration rate, but a slight increase in renal blood flow is frequently seen after administration of these agents. The greatest limitations to the use of these compounds are: (1) The limited potency (Figs. 2 and 4); (2) the development of acidosis, particularly in patients with renal damage; and (3) the development of tolerance with continued daily administration (Fig. 5). The latter limits the use of these compounds to milder states of sodium retention wherein a daily and persistent natriuretic response is not mandatory.

PHARMACOLOGY OF CHLOROTHIAZIDE

Diuretic Effect: Recently, chlorothiazide (Diuril®) was introduced for oral use[24] (Fig. 13). Chlorothiazide is an effective inhibitor of carbonic anhydrase *in vitro*. This does not appear to be the primary mechanism for producing diuresis, however. With effective diuretic doses, the increased rate of sodium excretion is nearly balanced by increased chloride excretion (Fig. 6). There is a lesser change in the rate of bicarbonate and potassium excretion and urinary pH.[25] The urinary electrolyte pattern is somewhat similar to that seen during mercurial diuresis (Figs. 1 and 6). At higher dosage levels,

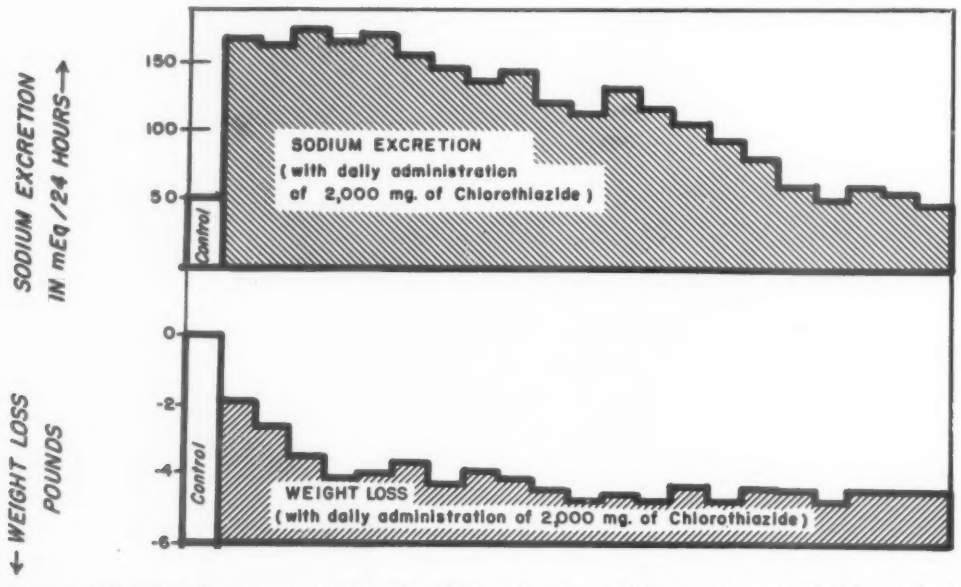

FIG. 7. *The effect of continuous administration of chlorothiazide on sodium excretion and weight loss.* Each block represents a twenty-four-hour period during continuous administration of chlorothiazide in the dose of 2,000 mg. a day. The patient continued to have a natriuretic response for approximately three weeks and then the sodium excretion gradually approximated the sodium intake. The weight loss was maintained due apparently to a reduction in extracellular fluid volume even when the sodium excretion approximated the intake.

the urine becomes alkaline from increased bicarbonate excretion that is characteristic of carbonic anhydrase inhibition in the renal tubules. Acidosis and resistance to the diuretic action does not develop on continued administration until there is a relative depletion of body sodium (Fig. 7).[26–28] When this occurs, the excretion rate approximates the sodium intake and the patient remains at dry weight. During diuresis caused by chlorothiazide, there is no significant change in glomerular filtration rate or renal plasma flow with therapeutic doses (Fig. 8). However, when the doses exceed 10 mg./kg., there is some depression in glomerular filtration rate which is only a temporary response.

In human bioassay studies[25] there is an increased diuretic response from this agent as the oral dose is raised to approximately 2,000 mg. (Fig. 9) whereas, when a dose of 250 mg. of the typical carbonic anhydrase inhibitors acetazolamide and ethoxzolamide has been given, increasing the amount administered produces little additional effect (Fig. 4).

The onset of action of chlorothiazide is prompt, indicating rapid absorption from the gastrointestinal tract. The action persists for about twelve hours after oral administration (Fig. 6). The response from divided doses is greater than from an equivalent amount given as a single dose.

Antihypertensive Effect: It was recently observed that chlorothiazide will enhance the response to antihypertensive agents.[29] For example, when chlorothiazide is given in conjunction with any of the ganglionic blocking agents, the dose requirement of the blocking agent is reduced 50 per cent or more in about three-fourths of the patients (Fig. 10). The mechanism whereby this is accomplished is not completely understood. However, similar effects, although not as pronounced, are also observed with other diuretic and natriuretic agents such as chlormerodrin when given continuously in adequate doses (Fig. 11) along with specific antihypertensive agents which depress sympathetic nervous system activity. In the case of chlorothiazide, the natriuretic effect is persistent and the side effects with chlorothiazide are less marked than those observed with the use of oral mercurial diuretics. This makes it more feasible to use this agent on a long term basis in conjunction with antihypertensive agents.

Chlorothiazide does not alter blood pressure in the laboratory animal (Fig. 8). It likewise fails to produce a significant reduction of blood

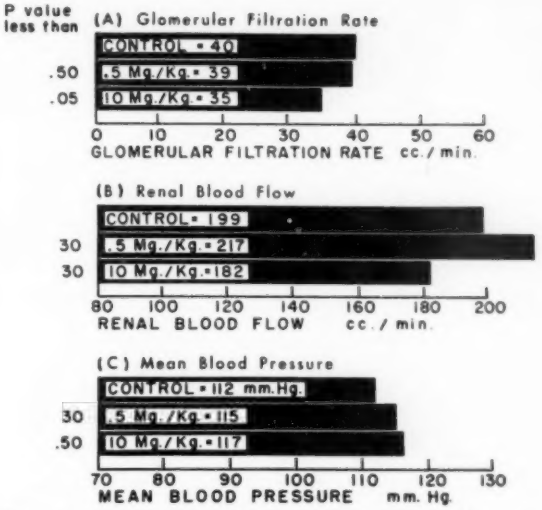

FIG. 8. *Renal hemodynamic response to chlorothiazide.* At smaller doses there was no effect on either glomerular filtration rate or renal blood flow. However, at doses exceeding 10 mg. per kg. given intravenously, there was a significant but temporary reduction in glomerular filtration rate. (From: Moyer, J. H., Ford, R. V. and Spurr, C. L. *Proc. Soc. Exper. Biol. & Med.*, 95: 529, 1957.)

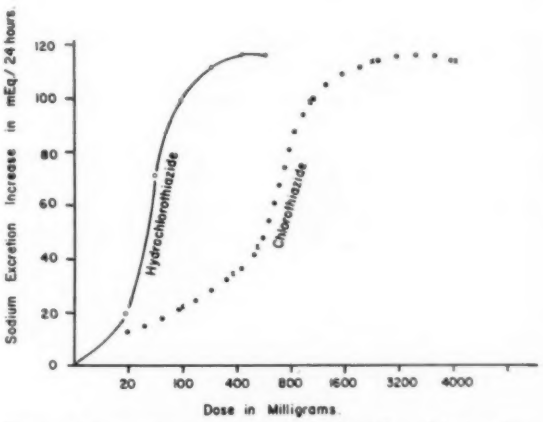

FIG. 9. *Dose response curves to chlorothiazide and hydrochlorothiazide.* The threshold dose of chlorothiazide appeared to be approximately 125 mg. whereas the threshold dose of hydrochlorothiazide was approximately 25 mg. The maximum effective dose of chlorothiazide appeared to be approximately 1,000 mg. given twice a day. At the maximum effective dose of each drug, the increase in sodium excretion was about the same.

pressure consistently in patients who are allowed a regular intake of salt and who are not receiving collateral specific antihypertensive agents. The drug is much more effective as an antihypertensive agent when given alone if the patient is placed on a highly restricted sodium intake. Freis[30,31] is of the opinion that chlorothiazide, through its diuretic action, decreases total blood

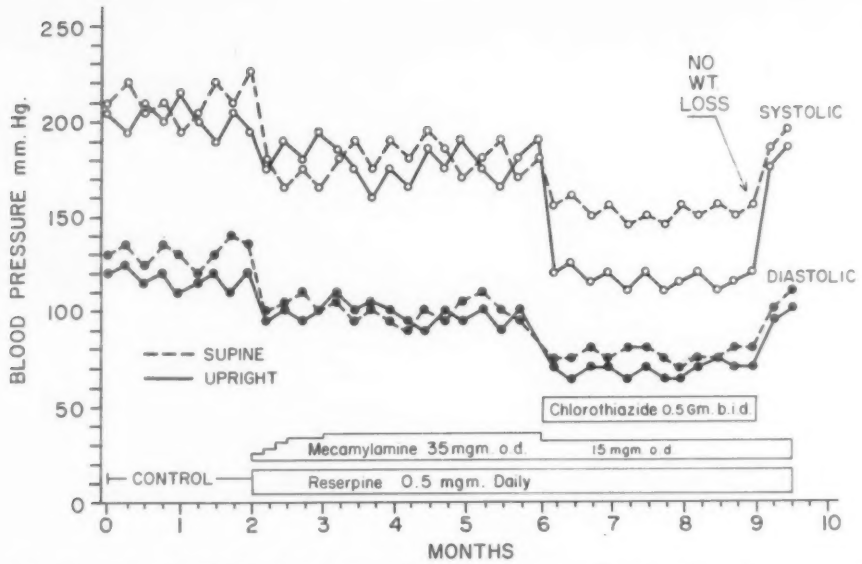

FIG. 10. *The effect of chlorothiazide on the blood pressure response to the ganglionic blocking agent mecamylamine (Inversine®) given in combination with reserpine.* Even at half the dose of mecamylamine the reduction in blood pressure was much greater when chlorothiazide was administered concurrently. When the chlorothiazide was discontinued, the blood pressure augmentation effect was lost. (From: Heider, C., Dennis, E. and Moyer, J. H. *Ann. New York Acad. Sc.*, 71: 456, 1958.)

volume thereby making ganglionic blockade more effective. On the other hand, the increased excretion of sodium produced by administration of chlorothiazide and the subsequent reduction in total body sodium could explain the potentiation of the drug (Fig. 7). The continuous administration of chlorothiazide reduces the vasopressor response to norepinephrine (Fig. 12) and supposedly to sympathetic nervous system stimulation since norepinephrine is the chemical mediator of neuroeffector transmission of vasoconstrictor impulses.[32] The role which the sodium ion plays in hypertension is undoubtedly important although not clearly defined.

Whatever the mechanism of its action, it appears that chlorothiazide is an important adjunct in the treatment of hypertension. It is still too early to evaluate the long term effect of this form of therapy on reduction of blood pressure.

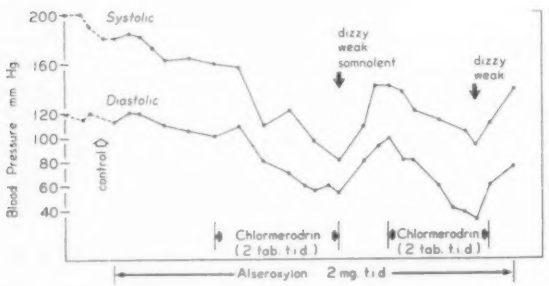

FIG. 11. *The effect of chlormerodrin on the blood pressure response to rauwolfia.* Chlormerodrin produces a significant additional reduction in blood pressure which was lost when the chlormerodrin was discontinued. The blood pressure response was reproduced when the chlormerodrin was started again. (Upright blood pressures recorded.)

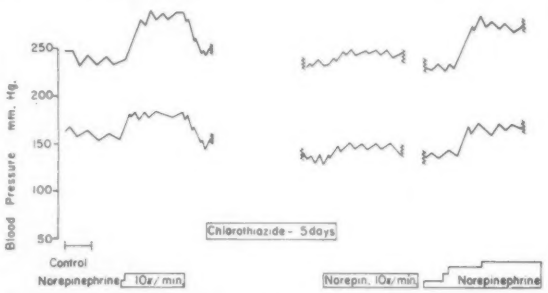

FIG. 12. *The effect of chlorothiazide on the blood pressure response to norepinephrine.* When norepinephrine was administered prior to the chlorothiazide a dose of 10 gamma per minute caused an increase in blood pressure of 40 mm. Hg systolic and 20 mm. Hg diastolic. After chlorothiazide was given for a period of five days the same dose of norepinephrine had no effect on blood pressure. When the infusion rate of norepinephrine was gradually increased to produce the same degree of blood pressure response, it was observed that the infusion rate required was 20 gamma per minute. This indicates that chlorothiazide decreases the vascular response to norepinephrine.

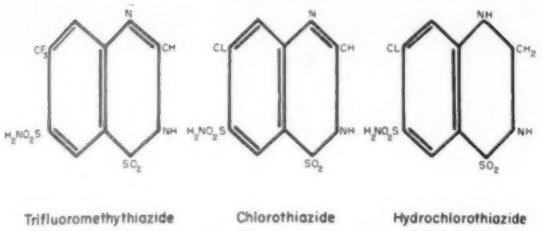

FIG. 13. Structural formulas for three thiazide derivatives.

PHARMACOLOGY OF NEWER THIAZIDE DERIVATIVES

The advance in diuretic therapy observed with chlorothiazide has stimulated the evaluation of other benzothiadiazine derivatives in an attempt to improve potency and decrease the incidence of side effects. Figure 13 contains the structural formulas of two such derivatives which have been studied extensively. Trifluoromethyl thiazide (flumethiazide)* differs from chlorothiazide in that the chloride atom on the benzene ring is replaced by a trifluorinated methyl group. Hydrochlorothiazide† has the same structure as chlorothiazide except that two hydrogens have been added.

FLUMETHIAZIDE

An evaluation of the effects of flumethiazide administered intravenously reveals similar responses in renal hemodynamics as with chlorothiazide.[33,34] Eight hundred mg. of this agent were administered orally to patients, and the excretion rates of water and electrolytes were determined. Glomerular filtration rate was determined concurrently by the inulin clearance method and renal plasma flow was estimated by the para-aminohippurate clearance technic.

Acute Effects: Following the administration of the drug the blood pressure was checked every few minutes for any immediate changes in blood pressure and then every thirty minutes for six hours. There was no change in the mean blood pressure in any of the patients throughout the study.

The excretion of sodium is shown in Figure 14. The onset of natriuretic activity occurred between the first and second hours after administration of the drug and reached its maximum effect by the end of the second hour. The duration of activity extended beyond the sixth hour of the study. There was no significant change in either glomerular filtration rate (Fig. 15) or the renal plasma flow during the period of study.

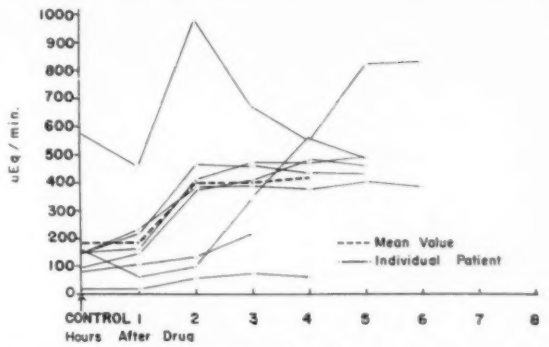

FIG. 14. *The effect of flumethiazide on sodium excretion*, following the oral administration of 800 mg. in eight patients.

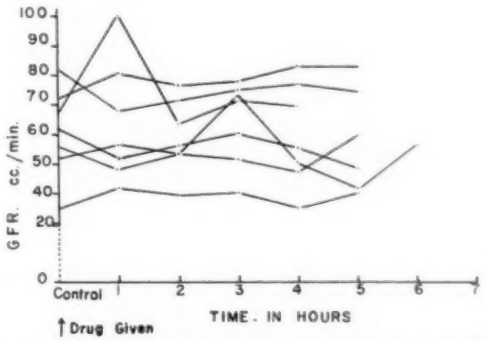

FIG. 15. *The effect of flumethiazide on glomerular filtration rate.* There was no significant and consistent alteration in glomerular filtration rate following the administration of 800 mg. of flumethiazide by the oral route to seven patients.

Dose Response Curves: Dose response curves were determined[33,34] in the outpatient clinic by determining the acute weight response after forty-eight hours in a group of cardiac patients who received increasing doses of the drug and in hospitalized patients on a standard 50 mEq. sodium intake. The increase in sodium excretion was used as the modality (natriuresis) for estimating response. In the study at the outpatient clinic, the patients were free of diuretic therapy between each dose of the drug for at least five days and were receiving maintenance doses of digitalis. A dose of 800 mg. given twice a day had the same effect on weight response in this group of patients as did a dose of 500 mg. of chlorothiazide given twice a day to the same group. When 1,000 mg. was administered twice daily the effect was the same as 1,000 mg. of chlorothiazide given twice daily. Therefore, the maximum effective dose of both drugs is the

* Available as ademol from E. R. Squibb & Sons, New York, New York.

† Available as hydrodiuril from Merck Sharp & Dohme, Inc., Philadelphia, Pennsylvania.

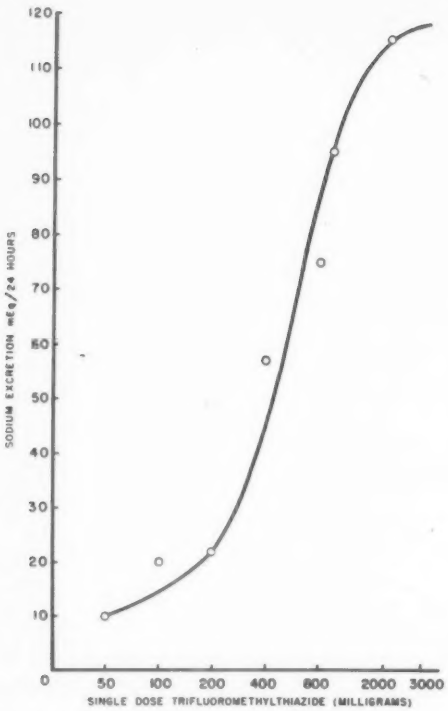

FIG. 16. *Dose response curve of flumethiazide*, using sodium excretion as a measurement of potency. The threshold dose appeared to be 125 mg. The maximum effective dose was approximately 2,000 mg. This response curve is quite similar to the response curve of chlorothiazide as shown in Figure 9.

same. Increasing doses above 1,000 mg. twice a day produces no further increase in effectiveness, as was previously observed with chlorothiazide.[25] When the increase in sodium excretion was used to determine the dose response, the observations summarized in Figure 16 were obtained. This response is almost identical with a similar study made on chlorothiazide (Fig. 9).

HYDROCHLOROTHIAZIDE

Studies of excretion[35,36] indicated that hydrochlorothiazide appeared in the urine within one hour after oral administration. At the end of six hours approximately 20 per cent of the total dose administered was excreted in the urine. The disposition of the remaining amount has not been determined. Maximum excretion was reached within three hours after administration and the plasma level reached maximum concentration within the first two hours and rarely exceeded 6 μg./ml. of plasma.

Acute Diuretic Effects: Hydrochlorothiazide was administered intravenously in a dose of 200 mg. Observations were made on glomerular filtration rate by the inulin clearance technic and renal plasma flow was determined by the use of para-aminohippurate. After three successive control periods were obtained the drug was administered and successive thirty-minute collections were made for five hours. Immediately following intravenous administration of the drug there was a temporary reduction in the glomerular filtration rate. This returned to control values within one hour. Despite the temporary decrease in glomerular filtration rate there was an increase in salt and water excretion. It can be concluded from these observations that the diuretic and natriuretic effect of the drug is a tubular response and is not due to an increase in glomerular filtration rate.

A measurement of the hourly urine response following the oral administration of a large oral dose of the drug showed a diuretic response beginning during the first hour with the maximum response during the third hour and a diuretic effect throughout the observation period of six hours or more. The same effect was demonstrated when the hourly increase in sodium and chloride excretion was compared with the control sodium and chloride excretion.

Electrolyte Excretion Studies: In order to determine the degree of response of electrolyte excretion to various doses of hydrochlorothiazide, eighteen patients were studied. These patients were put on a 50 mEq. sodium diet and control twenty-four–hour urines were taken for several days until a fixed twenty-four–hour sodium excretion (40 to 48 mEq.) was obtained. The patients were then given the drug for two days and twenty-four–hour urines were collected for determination of increased sodium, potassium and chloride excretion above control levels as in the studies on flumethiazide and chlorothiazide. The average of the first forty-eight–hour excretion was compared to the control. The patient was then allowed to equilibrate and replenish sodium stores again without the drug. Increasing doses were administered after a period of equilibration was obtained for control sodium excretion. The doses used were 25, 50, 100, 200, 400 and 800 mg. per twenty-four–hour period.

The dose response curve is graphed in Figure 17. It is noted that natriuretic activity starts at the 25 mg. dose level with a marked increase in electrolyte excretion at the 50 mg. dose level. There is an increasing electrolyte excretion up to 200 mg. above which the increased sodium excretion response levels off. In the effective dose

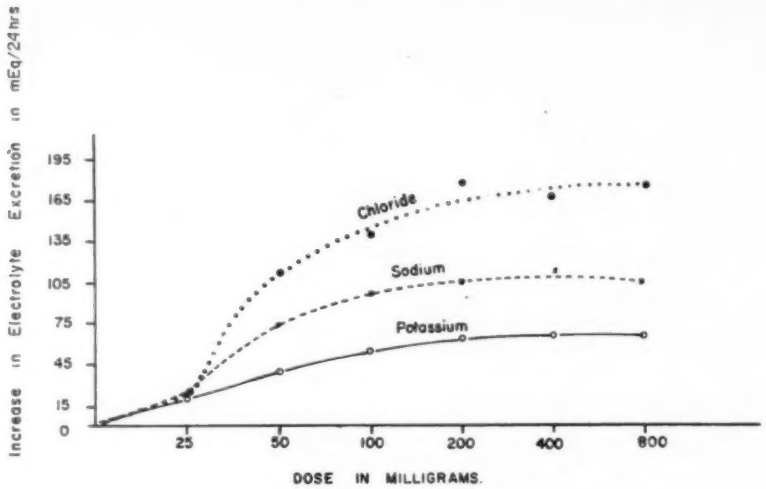

FIG. 17. *Dose response curve to hydrochlorothiazide* measuring sodium, chloride and potassium excretion rates. The primary effect appeared to be an increase in chloride excretion with a lesser effect on sodium excretion. There was a significant increase in potassium excretion as well.

range potassium loss is approximately one-half that of sodium and the most marked effect is on chloruresis which is greater than the natriuretic effect of hydrochlorothiazide.[37] This response is different from the response to chlorothiazide and a mercurial diuretic in which the sodium and chloride excretions are more nearly equal or the chloride excretion is less than sodium (Fig. 1).

The response to a single daily dose of 400 mg. compared to 200 mg. given twice a day is seen in Figure 18. The initial natriuresis was somewhat greater when the 400 mg. dose was given as compared to the 200 mg. dose. However, when the 200 mg. dose was repeated twelve hours later, an additional natriuretic response was observed. The total twenty-four–hour excretion rate of sodium was greater when the 400 mg. were given in divided doses (200 mg. b.i.d.) instead of a single dose.

Comment on Thiazide Derivatives

From the data presented it appears quite obvious that all three thiazide derivatives are efficient diuretic drugs. A study of the dose response curves reveals that the onset of activity of chlorothiazide and flumethiazide starts at the 250 mg. dose level and increases to the maximum effective dose of 2,000 mg. The onset of response with hydrochlorothiazide starts at 25 mg. and increases to a maximum effective dose of 200 mg. Therefore, in the effective dose range of

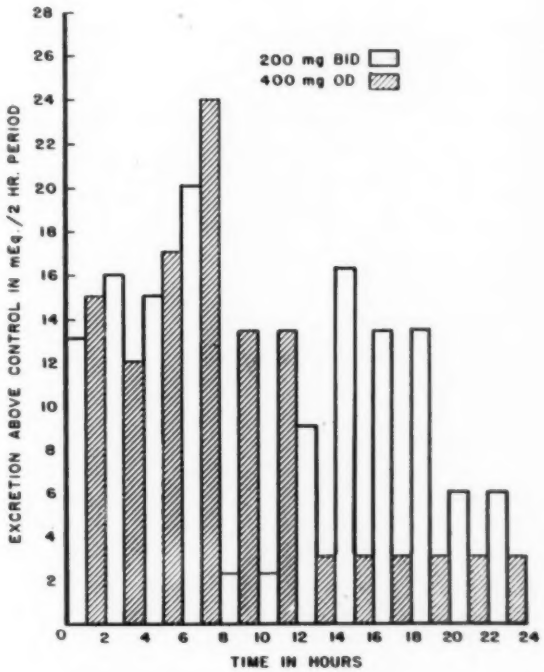

FIG. 18. *A comparison of the effect of hydrochlorothiazide on sodium excretion* using a dose of 400 mg. given as a single dose in a twenty-four–hour period as compared to 200 mg. given every twelve hours. Following a single dose of 400 mg. there was a greater initial increase in sodium excretion but due to the fact that the second 200 mg. dose of hydrochlorothiazide produces a secondary rise in sodium excretion, the twenty-four–hour total sodium excretion was greater when the drug was given in a divided dose of 200 mg. twice a day.

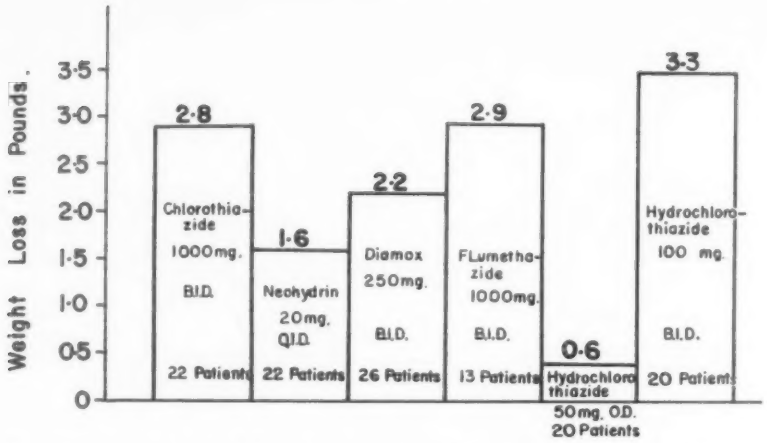

FIG. 19. *A comparison of the weight loss response* in a group of patients with congestive heart failure who were given the various drugs for a period of two days in the doses indicated in the graph. O.D. = once daily; B.I.D. = twice daily; Q.I.D. = four times daily.

these drugs a dose of hydrochlorothiazide which will produce a specific response is one-tenth that of chlorothiazide or flumethiazide. However, at the maximum effective dose level of each compound for diuresis the natriuretic effect is the same for all three drugs.

Hydrochlorothiazide also differs from the other two derivatives in that there is a greater chloruretic than natriuretic effect and potassium excretion is greater. This could result in a hypochloremic hypopotassemic alkalosis. Therefore, close observation for electrolyte imbalance must be maintained with the use of this agent as with the use of any potent drug of this kind.

The clinical response to these agents is demonstrated by the acute forty-eight–hour weight loss experienced in a group of patients with congestive heart failure in our diuretic clinic (Fig. 19). These patients were on maintenance digitalis therapy and were free of diuretic therapy for at least five days. It is shown that the weight loss experienced by these patients is the same when the maximum effective dose of chlorothiazide and flumethiazide was given. This response was greater than the response seen after an effective dose of chlormerodrin or acetazolamide was administered. When the maximum effective dose of hydrochlorothiazide was given, the weight response was greater than that observed with the other two thiazide derivatives; this could infer a greater clinical effectiveness. We have also seen rather efficient diuresis with hydrochlorothiazide in patients who have appeared refractory to chlorothiazide. This may not necessarily imply a greater diuretic activity for hydrochlorothiazide but may be a result of tolerance to chlorothiazide in those particular patients who are still responsive to hydrochlorothiazide. If so, then the factor of tolerance to one agent and not to the other may allow for more prolonged constant diuretic therapy by alternating these agents before or after tolerance starts to manifest itself.

The advancement made in the diuretic field has been dramatic with the discovery of these agents and future increased benefits will be anticipated with the investigation of other derivatives of the benzothiadiazine structure.

The Clinical Use of Diuretics

It should be remembered that diuretic agents are only one aspect of therapy for the treatment of patients with abnormal sodium and water retention. The diuretic is usually not a curative measure, rather these agents improve only the symptoms associated with abnormal sodium and water retention. Consequently, when possible, it is preferable to correct the basic physiologic defect.

Diuretics in the Treatment of Heart Failure

Mechanisms of Sodium and Water Retention and Edema: Sodium and water retention is a common pathophysiologic manifestation of diseases of diverse etiology. The management of congestive heart failure is only one area that has been significantly improved by the judicious use of diuretics. In the patient with heart fail-

ure several well known mechanisms operate to produce abnormal sodium and water retention; the final common pathway being direct and indirect effects on the kidney. One mechanism associated with the reduction in cardiac output is the reduction in renal blood flow and glomerular filtration rate which is followed by decreased sodium and water excretion and the development of occult edema.[38,39]

A second modus operandi in formation of edema associated with heart failure is the moderately increased venous pressure[40] and reduction in hepatic blood flow. This may result in a decrease in the hepatic inactivation of adrenal cortical salt-retaining hormones, particularly aldosterone. The relative increase of these hormones in the blood going to the kidneys stimulates the renal tubules to reabsorb more sodium, resulting in sodium retention.[41–43] Electrolyte retention can also cause stimulation of hypothalamic osmoreceptors which is followed by the secretion of additional antidiuretic hormone (ADH). The result is further retention of water and increased blood volume which results in a markedly increased venous pressure leading to manifest formation of edema. Other hormonal relations are as yet not clearly understood.

It is the resulting pathologic state of edema and its treatment that we are concerned with at this time. It is quite obvious that the one common denominator is the reduction in water and electrolyte excretion by the kidneys. It is therefore obvious that the aim of therapy in congestive heart failure is not only to improve myocardial function but also to achieve a block in the abnormal retention of sodium and water.

TREATMENT OF HEART FAILURE

Rest: In patients with heart failure, digitalis and decreased physical activity are of primary importance. Only when these more simple measures prove to be inadequate are diuretics indicated. When cardiac failure is severe, exercise reduces the glomerular filtration still farther, resulting in sodium and water retention.[44] Since glomerular filtration rate is highest when the patient is in the supine position at rest and decreases as the upright position is assumed, initially it is best to have these patients at rest in bed.

In using bed rest for the treatment of heart failure, this should be viewed as a temporary measure only since many secondary physiologic alterations follow excessively prolonged rest in bed. But, restricted activity should be advised as a permanent measure. Once heart failure has developed, it is rare that cardiac function returns entirely to normal irrespective of the etiology of the disease or the therapeutic program applied. Moreover, the more frequently and more severely a patient decompensates the more difficult it is to improve the cardiac status to anything near normal. Consequently, we believe that it is preferable to use maximum therapy rather than take a chance of undertreatment. Severe and progressive heart failure develops in many more patients from inadequate therapy than the number which have difficulty from the side effects associated with overtreatment.

Restricted Salt Intake: Sodium chloride intake should also be given primary consideration in many patients with edema.[45] Usually, water intake is of little importance so long as sodium intake is rigidly restricted. In fact, a large urinary volume will often promote an increase in sodium excretion.

Generally, the more severe the heart failure the less salt can be excreted by the kidney. Thus, in a patient with mild heart failure, restriction of salt intake to 3 gm. daily will be adequate. In patients with moderately severe heart failure, the daily salt intake should be restricted to less than 1.5 gm. In patients with severe heart failure, the salt intake should be restricted to less than 500 mg. per day. When effective diuretics are given continuously, the salt intake usually can be liberalized. For effective low salt diets the family and the patient should be instructed in the methods and virtues of a low salt diet by someone adequately trained in this field. This cannot be emphasized too much. It is not enough for the physician to merely instruct the patient to "go on a low salt diet." All too often, patients will go for years without proper dietary instruction.

Administration of Diuretics: Diuretics can be used as follows:

(1) Give a parenteral mercurial diuretic initially when heart failure is severe, e.g., meralluride, 2 cc. intramuscularly daily or mercaptomerin 2 to 3 cc. daily for three to five days until gross edema has disappeared.

(2) Chlorothiazide (Diuril) or flumethiazide (ademol) can be used in place of the mercurial in a dose of 1,000 mg. every eight to twelve hours or 100 mg. of hydrochlorothiazide (hydrodiuril) can be given every twelve hours. After the emergency is controlled, the dose should be

decreased to the minimally effective dose but no less than 250 mg. of chlorothiazide or 25 mg. of hydrochlorothiazide should be given every other day.

(3) *For maintenance therapy*, chlorothiazide or flumethiazide (250 mg. daily to 1,000 mg. twice a day) or hydrochlorothiazide (25 mg. daily to 100 mg. twice a day) may be given by the oral route. Oral mercurial diuretics such as chlormerodrin (Neohydrin), five to eight tablets daily, can be used also. *When heart failure is mild*, compensation may also be maintained with acetazolamide (250 mg.) or ethoxzolamide (250 mg.) or aminoisometradine (600 to 1,200 mg. per day) given every other day or daily for three consecutive days of each week. *In moderate to severe heart failure*, these compounds will rarely be adequate for maintenance therapy. Then chlorothiazide (250 to 1,000 mg. b.i.d.) or flumethiazide (250 to 1,000 mg. b.i.d.) or hydrochlorothiazide (50 to 100 mg. b.i.d.) or chlormerodrin (one to two tablets after each meal and at bedtime) must be used if the oral route of administration is to be employed. Otherwise, parenterally administered mercurial agents must be given in adequate doses (1 to 4 cc.) and as frequently as necessary to maintain the edema-free state. Diuretics used in this manner increase sodium and water excretion and thus decrease blood volume and venous return of blood to the heart. Right auricular filling pressure is thus reduced and cardiac output increases.

Diuretics in Premenstrual Edema and Edema of Pregnancy

The problem of premenstrual edema has been recognized as a syndrome resulting from hormonal imbalance. It is present in perhaps 40 per cent of women, and is associated with gain in weight, subcutaneous edema, emotional tension, breast turgidity and a state of anxiety and tension. It seems logical that the hormonal events of the last few days of the menstrual cycle result in either a direct or indirect effect on the renal tubules by an increase in tubular absorption of sodium and water.[46–48]

Edema of pregnancy may be seen as an exaggeration of a pre-existing disease such as congestive heart failure, nephritis, etc., or it may be the manifestation of an impending toxemia of pregnancy. It is to be remembered, however, that even during normal pregnancy the blood volume increases from 30 to 50 per cent and that there is a positive salt balance (retention of salt and water) that reaches a maximum by the thirty-sixth week of gestation. Whatever the interrelated factors in edema of pregnancy may be, the common denominator is, once more, increased tubular reabsorption of sodium and water which can be blocked by appropriate diuretic therapy.

Treatment of Premenstrual Edema: The desired effect is to increase sodium and water excretion. Edema is not marked in this disease entity. An outline of therapy is as follows:

1. During the last five to seven days of the menstrual cycle: (a) low sodium diet; (b) chlorothiazide or flumethiazide in a dose of 500 mg. twice a day or hydrochlorothiazide, 50 to 100 mg. daily, or acetazolamide, 250 mg. (one tablet) or ethoxzolamide, 125 mg. (one tablet) daily.

Treatment of Edema of Pregnancy: The desired effect is to decrease sodium and water retention. Since pre-existing disease may be responsible for edema in this entity, a close medical survey must be completed. When no obvious causes of edema are found, then therapy may be summarized as follows:

(1) At first sign of edema: low sodium diet.

(2) If not controlled by diet; chlorothiazide,* 500 to 1,000 mg. twice a day or acetazolamide, 250 mg. or ethoxzolamide, 125 mg. may be given every other day if edema is not marked.

Edema Associated with Renal Disease

Factors Causing Salt and Water Retention: In the nephrotic syndrome not only does the factor of decreased glomerular filtration and renal blood flow result in a decreased sodium excretion, but also an excessive loss of protein in the urine occurs. This results in decreased colloid osmotic pressure of the blood, an additional cause for fluid loss to the tissues.[49] Thus, not only is there a need for a natriuretic agent but also better results may be obtained frequently by an agent which increases the plasma osmotic effect, such as salt-poor human albumin administered intravenously. Albumin sometimes appears to have a natriuretic and diuretic effect on the kidney which is unrelated to its osmotic activity. Heightened mineral corticoid activity, increased pituitary secretion of antidiuretic substances, and osmotic shifts of fluid and electrolytes have all been cited individually

* Flumethiazide and hydrochlorothiazide can probably be used here but this has not been studied by the authors.

as mechanisms producing salt and water retention in nephrosis. Possibly all of these factors are involved.

Treatment: The treatment may be summarized as follows:

(1) Bed rest.

(2) Low sodium diet.

(3) Chlorothiazide or flumethiazide, 500 to 1,000 mg. b.i.d. or hydrochlorothiazide, 50 to 100 mg. b.i.d.

(4) If the first three therapeutic procedures do not control edema in one week, a seven-day trial of ACTH administered intravenously as 25 units in 1,000 cc. of 5 per cent dextrose in water over an eight-hour period daily or as "gel," 40 units given intramuscularly every twelve hours, may be tried. Ten mg. of prednisone may be given every six hours for four doses, then 5 mg. every six hours for eight doses, then 5 mg. every twelve hours for eight doses as an alternative. Diuresis usually occurs as the steroid (or ACTH) therapy is withdrawn. The mechanism is poorly understood. We have noted that maximum diuresis can be obtained when administration of chlorothiazide or hydrochlorothiazide is started just as the steroid is withdrawn. For this purpose 500 to 1,000 mg. of chlorothiazide should be given every eight to twelve hours. The drug should be started on the last day of steroid administration and continued thereafter as long as the diuretic and natriuretic effect is desired.

(5) If there is no response to the aforementioned regimens, administer 100 gm. of salt-poor human albumin intravenously every other day. This is an expensive procedure.

(6) Finally, parenteral mercurials (meralluride, 1 to 2 cc. daily) may be tried when edema is severe and unresponsive to the measures outlined previously.

Diuretics in Hepatic Disease

Hepatic disease presents the problem of disordered protein formation which results in a decreased colloid osmotic pressure of blood. This requires the use of an osmotic diuretic such as salt-poor human albumin intravenously. There may be a decreased inactivation of salt-retaining steroids which results in sodium and water retention. At the present stage of our knowledge this can be controlled only by a natriuretic agent.

Treatment: Since the edema usually is associated with inadequate protein formation with reduction in blood osmotic pressure, the underlying liver disease should be treated actively. However, other factors such as decreased hepatic inactivation of salt-retaining steroids may be treated by agents acting to block the renal tubular reabsorption of sodium. Thus, treatment for edema or ascites may be outlined as follows:

(1) Low sodium diet and decreased physical activity.

(2) In presence of significant hypoalbuminemia (serum albumin less than 3 gm. per cent) give a high protein diet and may use salt-poor human albumin, giving 100 gm. intravenously every other day to achieve diuresis. The expense may be a contraindication here.

(3) Increase sodium and water excretion by giving meralluride, 2 cc. intramuscularly daily as needed to control massive edema.

(4) If response to meralluride is not adequate give chlorothiazide or flumethiazide, 500 to 1,000 mg. every eight hours or hydrochlorothiazide, 100 to 200 mg. every twelve hours.

(5) After massive edema is controlled, maintenance therapy may be continued with chlorothiazide or flumethiazide, 500 to 1,500 mg. daily by mouth or hydrochlorothiazide, 50 to 200 mg. daily. Use the smallest effective dose.

Treatment of Iatrogenic Edema

The increasingly common syndrome, "iatrogenic steroid edema" results from the therapeutic use of steroids such as cortisone, hydrocortisone, prednisolone and prednisone. They affect the kidney to induce edema indirectly by the enhancement of renal tubular reabsorption of sodium. Diuretic agents, particularly chlorothiazide and the organomercurials, have been particularly helpful in the management of this complication.

Treatment: When sodium retention and edema become a problem it is preferable to discontinue the steroid but this is not always possible. In the latter case, the edema can usually be treated by daily and continuous administration of chlorothiazide,* 500 to 1,000 mg. every eight hours, or chlormerodrin, two tablets four times a day. When these agents are not adequate when given alone, they should then be given in combination.

Parenteral meralluride is also effective but when used for this purpose it must be given every twelve hours since the maximum increase

* Flumethiazide and hydrochlorothiazide are probably also effective but have not been studied by the authors.

in sodium excretion occurs during this period. During the subsequent twelve-hour period (when the drug is not given again) there is actually retention of sodium.

Summary

In discussing some of the more common clinical syndromes of edema, we note that renal retention of sodium and water is a common denominator but that other factors such as decreased colloid osmotic pressure of the blood, decreased blood flow to the liver and decreased or abnormal hormonal activity may be the primary event and must be given primary therapeutic consideration. It is also seen that in varying degrees of importance, natriuretic (or diuretic) agents are a therapeutic common denominator for the treatment of symptoms associated with excessive sodium and water retention.

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New Methods

Left Ventricular Angiocardiography in the Diagnosis of Persistent Atrioventricular Canal and Related Anomalies*

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WHEN operation is contemplated in a patient with an intracardiac left-to-right shunt, the exact anatomic lesion or combination of lesions present must be clearly defined. At the present time the results of surgical treatment are largely dependent upon the specific malformation present, since the various defects are not equally amenable to complete correction or closure and the mortality rates vary accordingly. In many patients with isolated, uncomplicated atrial or ventricular septal defects careful clinical examination and conventional catheterization technics are sufficient to supply the requisite information. When the clinical and catheterization findings are atypical or equivocal, however, the presence of a more complex anomaly must be suspected. Among these are combined atrial and ventricular septal defects of the usual varieties, left ventriculo-right atrial communication and the various forms of persistent atrioventricular canal.

CLINICAL FINDINGS SUGGESTING A-V CANAL

The clinical and hemodynamic profile of the more usual ostium secundum and sinus venosus types of atrial septal defect are well recognized.[1,2] In a patient who is suspected of having an atrial septal defect, certain clinical findings may be present to suggest that the lesion is one of the more complex varieties. These findings include a prominent left ventricular tap, a systolic thrill at the apex or lower sternal border and a loud holosystolic murmur at either of these areas. Since severe pulmonary hypertension is relatively uncommon in patients with atrial septal defect,[3] particularly in children, the presence of a markedly accentuated pulmonary second sound on palpation and auscultation is also suggestive. The electrocardiogram provides important but not infallible aid. P-R prolongation is frequent in patients with varieties of A-V canal.[4,5] Left axis deviation or a spatial vectorcardiogram which, in the frontal plane, is oriented superiorly, to the left, and has a figure-of-eight configuration also is frequently recorded in such patients. Left ventricular hypertrophy with a normal axis, on the other hand, is observed commonly in ventricular septal defect but rarely in the usual types of atrial septal defect. Similarly, radiographic evidence of left ventricular hypertrophy should cast doubt upon this diagnosis.

INDICATOR DILUTION CURVES

At the National Heart Institute, cardiac catheterization is performed preoperatively in all patients with intracardiac shunts. When an interatrial communication of any type is considered likely, the catheter is introduced from the saphenous rather than an antecubital vein. This approach always permits passage of the catheter into the left atrium and generally into the left ventricle if such a defect is present. The site of entry of the shunt is localized and the pulmonary to systemic flow ratio is determined by N_2O or krypton^{85} tests.[6–8] When one or more of these clinical, electrocardiographic or radiographic findings indicates the likelihood of a combined lesion, preparation is

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always made for a detailed assessment of the routes of left ventricular outflow. Indicator dilution curves recorded from a systemic artery following injections into the left heart[9] provide a convenient and accurate means for determining whether or not left ventricular blood is shunted, by any route, into the right heart and pulmonary circulation. Thus, if the curve recorded following left ventricular injection is unequivocally normal, any type of interventricular septal defect, a left ventriculo-right atrial communication and mitral valvular regurgitation combined with an atrial defect, is effectively excluded. A curve, however, which demonstrates an abrupt interruption and prolongation of its descent and fails to return promptly to its baseline constitutes strong evidence for the presence of one of these lesions. While an abnormal curve indicates that left ventricular blood is shunted into the pulmonary circulation it does not identify the specific anatomic defect responsible for the shunt. This information is provided by selective angiocardiography with left ventricular injection.[10]

LEFT VENTRICULAR ANGIOCARDIOGRAPHY

The majority of patients with congenital heart disease in whom left ventricular angiocardiography is indicated have some type of interatrial communication, and the catheter can be passed into the left ventricle through it. If the interatrial septum is intact, the angiography catheter is usually passed across the aortic valve and into the ventricle from the femoral or right radial artery. With local anesthesia the tip of the N.I.H. catheter* is positoned near the apex of the heart under fluoroscopic control and its position verified by pressure tracings and biplane roentgenograms. The patient is then anesthetized and rendered apneic by an injection of Pentothal and succinylcholine. Hyperventilation is furnished with a face mask until the time of injection when the lungs are held in forceful deep inspiration. This provides adequate oxygenation and the increased intrathoracic pressure effectively slows the passage of dye through the circulation. Urokon® 70 per cent has been the only contrast agent employed and doses of 1 to 1.2 cc./kg. body weight are usual. The dye is delivered through the catheter by a pressure syringe which permits the injection of 50 cc. of Urokon through a No. 8 catheter in less than one second. Biplane films are exposed at a rate of 4 to 6 per second.

The application of left ventricular angiography in the study of patients with atrial septal defect, ventricular septal defect, combined lesions and forms of persistent atrioventricular canal, are illustrated. Its usefulness in the preoperative recognition of left ventriculo-right atrial communication has been presented elsewhere in detail.[12]

CASE REPORTS

CASE 1. *Atrial Septal Defect of the Usual Type:* E. S., a five year old boy, presented with the classic history and physical findings of atrial septal defect. The electrocardiogram demonstrated right axis deviation but was suggestive of left ventricular hypertropy since there was an R wave in lead V_6 of 36 mm.

Cardiac catheterization confirmed the presence of a left-to-right shunt entering the right atrium and the catheter traversed an atrial septal defect and was passed into the left ventricle. Indicator dilution curves from the left ventricle were normal but because of the electrocardiographic evidence of left ventricular hypertrophy, it was thought that a malformation more complex than the usual type of atrial septal defect might be present.

An angiocardiogram with left ventricular injection was carried out (Fig. 1). There was no radiographic evidence of mitral regurgitation or of an interventricular communication. An uncomplicated septum secundum type of atrial septal defect was found and closed at subsequent open operation.

CASE 2. *Incomplete Persistent A-V Canal:* J. S., a thirty-six year old woman, presented with symptoms of diminished cardiac reserve. On physical examination both left and right ventricular hypertrophy were evident. An ejection type systolic murmur was heard over the pulmonary area but a distinctly different holosystolic murmur was present at the apex. The electrocardiogram was considered compatible with A-V canal.

At catheterization there was marked pulmonary hypertension and evidence of a left-to-right shunt entering the right atrium. Indicator dilution curves from both the left atrium and ventricle were abnormal, indicating that left ventricular blood contributed to the shunt.

The left ventricular angiocardiogram (Fig. 2) revealed gross mitral regurgitation and an intact ventricular septum. The lesion was thus classified as an incomplete form of A-V canal and at open operation the cleft leaflet of the mitral valve was closed and the septum primum defect above it repaired with a prosthesis.

* Manufactured by the U. S. Catheter and Instrument Co., Glens Falls, New York.

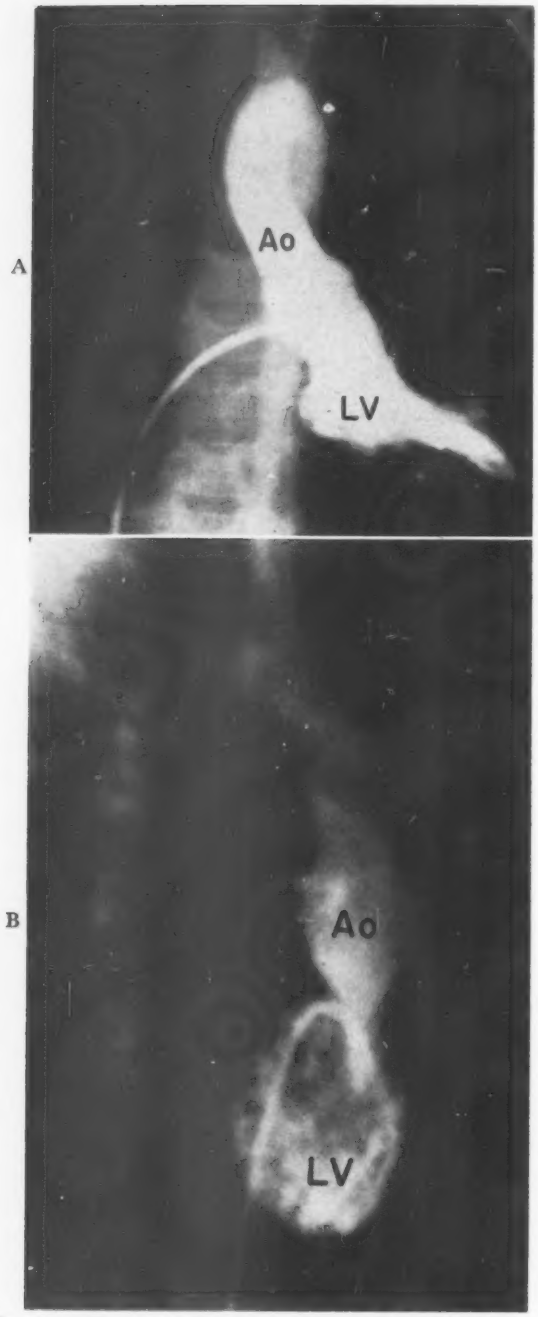


FIG. 1. Case 1. *Uncomplicated Atrial Septal Defect.* Anteroposterior (A) and lateral (B) views of the left ventricular angiogram. The left ventricle (LV) and aorta (Ao) are well opacified and there is no left atrial or right ventricular filling. An incidental finding is absence of the right coronary artery.

CASE 3. *Incomplete Persistent A-V Canal:* N. R., a thirty-four year old woman, had had several attacks of rheumatic fever during childhood. On clinical examination she was considered to have mitral regurgitation secondary to rheumatic fever. The roentgenogram revealed both left atrial and left ventricular enlargement and the electrocardiogram demonstrated atrial fibrillation, a normal axis and left ventricular hypertrophy.

Surprisingly, cardiac catheterization revealed clear evidence of a left-to-right shunt entering the right atrium but there was no pulmonary hypertension. The catheter crossed an interatrial septal defect and indicator dilution curves from both the left atrium and left ventricle were abnormal. The selective left ventricular angiocardiogram (Fig. 3) again revealed gross mitral regurgitation into a greatly dilated left atrium. The ventricular septum was intact and right atrial opacification occurred from the left.

At open operation the interatrial communication was small and the anterior leaflet of the mitral valve was characteristically cleft. Both components of the defect were repaired. Anatomically and physiologically, mitral regurgitation appears to have been the predominant abnormality.

CASE 4. *Complete Form of Persistent A-V Canal:* W. L., a ten year old boy, had been known to have heart disease since his birth. His growth and development had been markedly retarded and he had experienced increasing exertional dyspnea during the year before admission. On physical examination there was evidence of biventricular enlargement and a prominent systolic murmur accompanied by a thrill was present at the apex. There was also electrocardiographic evidence of biventricular hypertrophy, left axis deviation and an RSR′ pattern in lead V_1.

Cardiac catheterization revealed marked pulmonary hypertension and a large left-to-right shunt entering the right atrium. The possibility of a second and smaller shunt entering the right ventricle could not be excluded. These findings suggested the presence of some form of persistent A-V canal and a selective left ventricular angiocardiogram was performed. A small interventricular communication was shown and there was gross regurgitation from the left ventricle into the left atrium (Fig. 4).

At subsequent open operation the typical complete form of persistent A-V canal was present. The large defect in the interatrial septum was repaired by prosthesis after the cleft mitral and tricuspid valves had been sutured. The interventricular communication measured only 3 mm. in diameter and it was not closed.

CASE 5. *Complete Form of Persistent A-V Canal:* S. P., a ten year old Mongoloid child, had a heart murmur which was discovered in infancy, but had remained without cardiac symptoms. The child was obese and no thrills were palpable. Grade 2/6 systolic murmurs were present at the apex and over the pulmonary area. Roentgenograms of the chest revealed enlargement of both ventricles and the electrocardiogram was considered consistent with A-V canal.

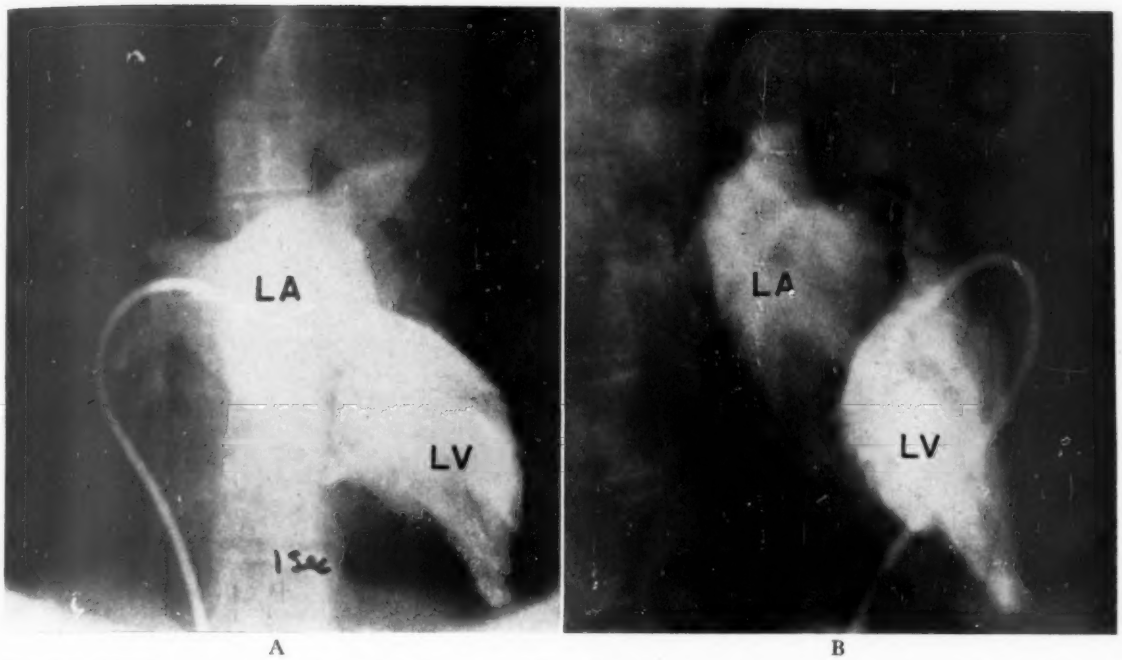


FIG. 2. Case 2. *Incomplete Presistent A-V Canal with Mitral Regurgitation.* Anteroposterior (A) and lateral (B) projections of the left ventricular angiogram. The left atrium (LA) and pulmonary veins are filled from the left ventricle (LV). The interventricular septum is intact.

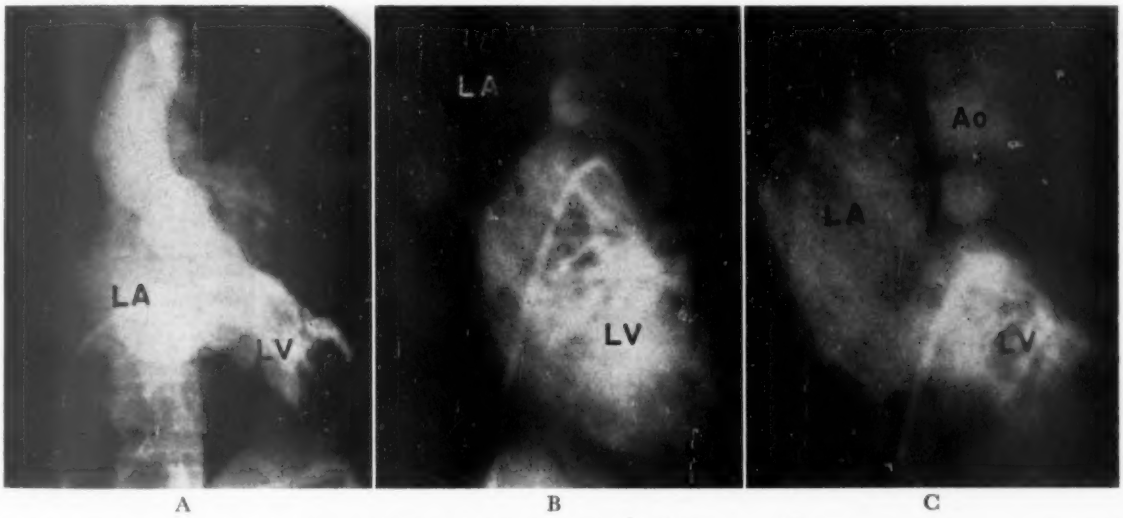


FIG. 3. Case 3. *Incomplete Persistent A-V Canal With Gross Mitral Regurgitation.* The anteroposterior projection (A) of the angiogram shows gross mitral regurgitation into a hugely dilated left atrium (LA). During ventricular diastole (B) the large left ventricular cavity (LV) is well visualized and the increased left atrial opacification during systole is shown in the slightly later exposure (C).

At cardiac catheterization mild pulmonary hypertension was present and a large left-to-right shunt was found to enter the right atrium. Again the presence of a second shunt distal to the tricuspid valve could not be excluded. Indicator dilution curves recorded following right ventricular injection confirmed the presence of a large left-to-right shunt. The catheter was passed across the interatrial septum and curves following left atrial and left ventricular injection were both abnormal.

A left ventricular selective angiocardiogram (Fig. 5) was performed, revealing a large interventricular

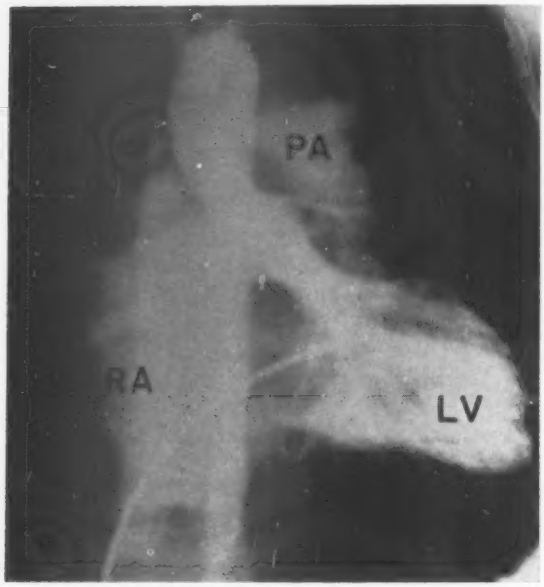
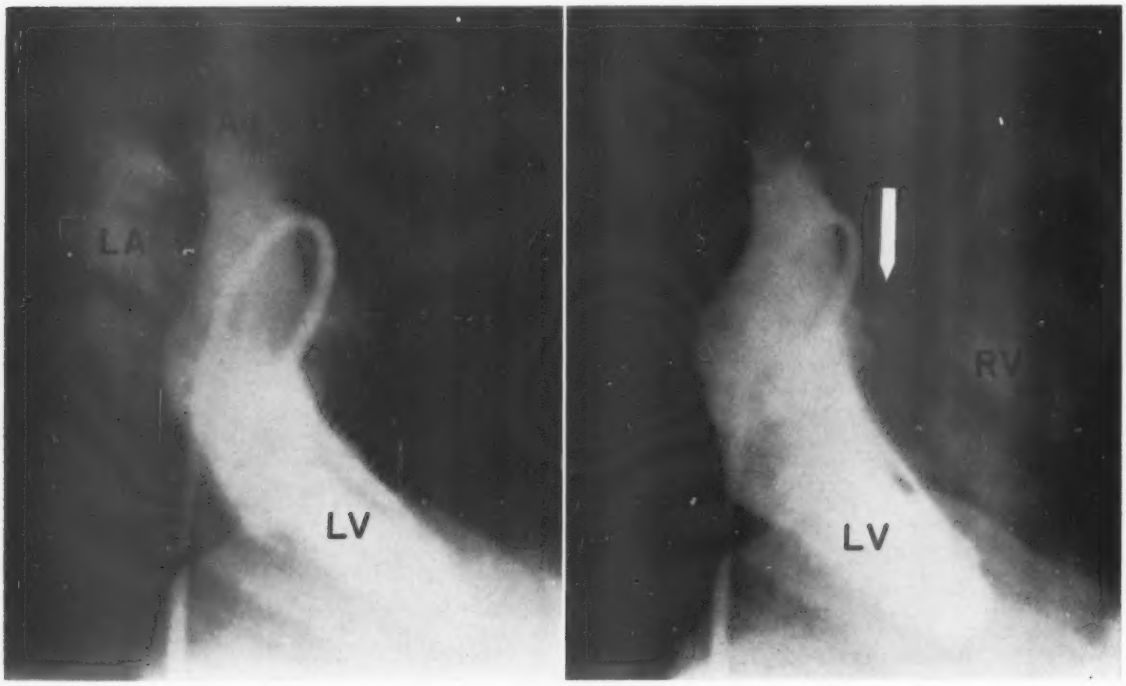


FIG. 4. Case 4. *Complete Persistent A-V Canal.* The anteroposterior view of the left ventricular angiogram demonstrates opacification of the right atrium (RA) and pulmonary artery (PA). The lateral views (not shown) revealed both mitral regurgitation and a small interventricular communication.

communication, gross mitral incompetence and opacification of the right atrium from the left. The lesion has been classified as a complete form of persistent A-V canal, but operative intervention has not been recommended because of the patient's general status.

CASE 6. *Ventricular Septal Defect of the Usual Type:* R. M., a four month old infant, had been in congestive heart failure since birth and had had repeated bouts of pneumonia. All of his short life had been spent in hospitals and his weight on admission was only 2.7 kg. On physical examination he appeared to be critically ill but was acyanotic. There was extreme tachycardia, cardiomegaly and a loud systolic murmur was audible over the entire precordium. Roentgenograms revealed hypervascular lung fields and generalized cardiac enlargement. The electrocardiogram demonstrated right axis deviation and biventricular hypertrophy.

At right heart catheterization there was moderate pulmonary hypertension and evidence of a large left-to-right shunt. The catheter could not be manipulated through an atrial septal defect. To determine the origin of the shunt, 30 μc. of Kr^{85} were injected into the left ventricular cavity by means of percutaneous puncture. The isotope appeared immediately in expired air proving that left ventricular blood was being shunted into the pulmonary circula-



A B

FIG. 5. Case 5. *Complete Persistent A-V Canal.* Lateral views of the left ventricular angiocardiogram. The earlier exposure (A) clearly demonstrates mitral regurgitation and that made one-third second later (B) reveals a large interventricular communication (arrow) and right ventricular filling (RV).

tion.[13] To further characterize the lesion a selective left ventricular angiocardiogram was carried out, again by means of percutaneous puncture. Urokon, 3.5 cc., was employed and a large interventricular septal defect was demonstrated (Fig. 6).

At operation an intense systolic thrill was palpable over the outflow tract of the right ventricle. Pulmonary stenosis was produced by constriction of the main pulmonary artery and the child's response to operation has been gratifying.

CASE 7. *Combined Atrial and Ventricular Septal Defects:* C. S., a sixteen year old girl, had been known to have heart disease since birth and had had numerous attacks of pneumonia and infection of the respiratory tract. Her growth and weight gain had been poor and she had had several episodes of cyanosis. Physical examination indicated right ventricular enlargement; a pulmonic ejection sound and a systolic murmur were audible to the left of the sternum. There was slight cyanosis and clubbing. Roentgenograms demonstrated enlargement of both ventricles with extreme prominence of the pulmonary artery and hypervascularity of the lungs. The electrocardiogram indicated enlargement of all chambers.

At cardiac catheterization identical pressures were recorded from the pulmonary artery and a systemic artery. A large left-to-right shunt entered the right atrium. Indicator dilution curves confirmed the presence of a large left-to-right shunt and demonstrated a small right-to-left shunt originating from the right ventricle. Dye curves from the left atrium and left ventricle were abnormal.

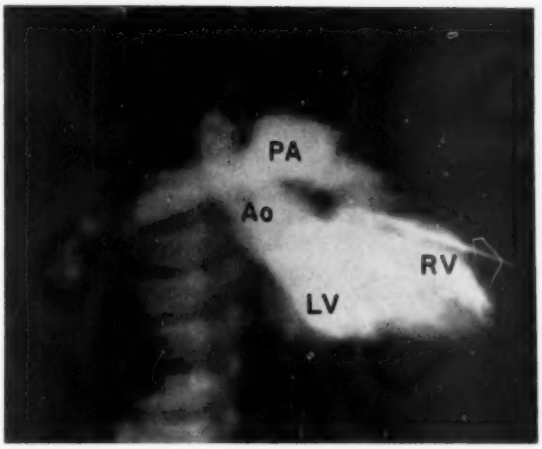
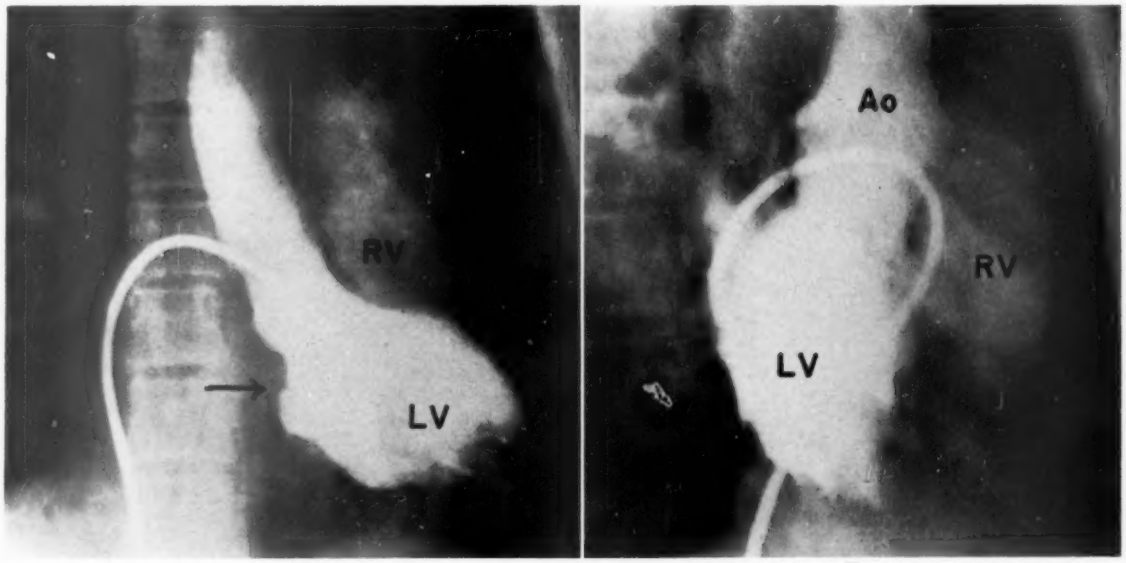


FIG. 6. Case 6. *Large Ventricular Septal Defect.* Anteroposterior view of the left ventricular angiocardiogram. The needle tip lies close to a large ventricular septal defect and both ventricles and great vessels are filled.

The selective left ventricular angiocardiogram (Fig. 7) demonstrated the presence of a ventricular septal defect and showed the mitral valve to be competent. The right atrium did not opacify. The presence of a separate atrial septal defect was indicated by the passage of the catheter across the septum and the strongly positive nitrous oxide test in the right atrium. It is clear that this patient has combined atrial and ventricular septal defects. Since the mitral valve is competent, however, the lesion apparently does not



A B

FIG. 7. Case 7. *Combined Atrial and Ventricular Septal Defects.* Anteroposterior (A) and lateral (B) views of angiocardiogram. The left ventricle (LV) and the right ventricular outflow tract (RV) are opacified. The mitral valve is clearly shown (arrow) and is competent. It is evident that mitral regurgitation is not produced by the catheter.

represent a variety of A-V communis. Operation has not yet been carried out.

Summary

The usefulness of left ventricular selective angiocardiography and indicator dilution curves in the study of patients with persistent atrioventricular canal and related complex defects is described. These studies permit precise preoperative diagnosis and their application is indicated when clinical or catheterization findings are considered atypical. The value of the technics is illustrated by selected clinical examples.

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Historical Milestones

Functional Heart Disease in the Civil War (Da Costa, 1871)

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AMONG the medical advances which were made as a result of the Civil War at least two are widely remembered today. These are the development of the concept of causalgia by Silas Weir Mitchell and the formation of the concept of irritable heart, later known as neurocirculatory asthenia, by Jacob M. Da Costa. The latter forms the theme of the present paper.

By the middle of the nineteenth century a large amount of information had been accumulated about the heart and its diseases. Systematic methods of physical examination had been devised which are still in use today. These were supplemented by simple mensuration and by measurement of the pulse rate and respiratory rate; no other instrumental technics were available. With the lack of such distracting methods as sphygmomanometry, roentgenology and electrocardiography, physical examination tended to be more detailed and accurate than it is today. Much had been learned about the morbid anatomy of the cardiovascular system, and the knowledge had been effectively correlated with clinical phenomena. At the same time numbers of symptoms had become grouped into syndromes and many well characterized disease entities had been formulated. Thus the art of clinical diagnosis had reached an advanced stage.

With regard to diseases of the heart these advances, based on morbid anatomy, were dominated by the search for organic ailments. Da Costa's study of the condition which he named irritable heart was an attempt to cross the frontier into the obscure realm of functional disease. A similar effort was made at about the same time by Morse K. Taylor.*

* See JARCHO, S. Morse K. Taylor on heart disease in the Civil War (1867). *Am. J. Cardiol.*, 4: 240, 1959.

Jacob M. Da Costa (1833–1900) was born in St. Thomas in the West Indies. After preliminary education in Germany he studied medicine at Jefferson Medical College in Philadelphia. For a time he was a pupil of the illustrious Trousseau in Paris. He was the author of a standard treatise on diagnosis, and in the opinion of F. H. Garrison was probably the most able clinical teacher of his time in the Eastern states.

The important paper which is excerpted herewith is titled "On Irritable Heart; a Clinical Study of a Form of Functional Cardiac Disorder and Its Consequences." The article appeared in the *American Journal of the Medical Sciences*, volume 61, pages 17–52, 1871. Thanks are due to Lea & Febiger, publishers, for permission to reprint excerpts from the text.

* * *

EXCERPTS FROM DA COSTA ON IRRITABLE HEART

In this paper I propose to consider a form of cardiac malady common among soldiers, but the study of which is equally interesting to the civil practitioner, on account of its intimate bearing on some obscure or doubtful points of pathology. Much of what I am about to say I could duplicate from the experience of private practice; yet I prefer to let this inquiry remain as it was originally conducted on soldiers during our late war. The observations here collected were made on a series of upwards of three hundred cases. That so large a number were examined is thus explained. Shortly after the establishment of military hospitals in our large cities, I was appointed visiting physician to one in Philadelphia, and there I noticed cases of a peculiar form of functional

disorder of the heart, to which I gave the name of irritable heart—a name by which the disorder soon became known both within and without the walls of the hospital. In a communication addressed to the Department in December, 1862, I further called attention to this form of cardiac malady, more particularly as it was observed subsequent to the Peninsular campaign. Afterwards, through the fostering care of the Medical Directors and Inspectors of this Military District, and the liberality and kindly interest of the Department at Washington, most of the cases of the kind were sent to my wards, thus enabling me to study the affection on a large scale. Some of the general facts recognized by this investigation I published in April, 1864, in the first edition of my "Medical Diagnosis"; but it was a mere outline, and the inquiry being pursued further, I intend here to give the complete results. The publication of the paper so long after the observations were made has been delayed by several causes; partly by want of leisure to analyze critically so large a number of cases; partly because it was my original intention to have offered this contribution as a report to the official history of the war; but chiefly because I found that, as I still from time to time encountered my former patients, I should by waiting have the opportunity of ascertaining the sequel to many of the cases recorded. And this—for reasons which will soon become evident—struck me in the examination of the subject as of particular value.

The class of cases which I am about to analyze was encountered in every army of the United States, and attracted the attention of many of its medical officers. Yet it cannot be said that ours was the first war in which it was noticed; for we find in the British Blue Book of the Crimean war, in the Report of the Hospitals of the Army in the East, as separate from morbus cordis, or carditis, pericarditis, etc., forty-five admissions for palpitation, and in another table, giving the return "invalided to England," sixty-two cases are thus classed; and I have seen here and there short statements which make it likely that the same affection was noticed in India, among Sir Henry Havelock's gallant troops. Nor can I believe that it has not always existed. Looking at the causes which produce it, it must have occurred among the troops in Sir John Moore's retreat, where, as Napier tells us, some brigades covered the retreat, fighting for twelve days, and traversed eighty miles of road in two marches; or among the devoted band by whose energetic movements Lord Clive conquered India; or among the victorious columns which, under Napoleon's guidance, passed by forced marches from the Rhine to the Danube, and compelled, at Ulm, the surrender of an army, or among the shattered and harassed forces which found their way back from the disastrous invasion of Russia. Yet, in examining, so far as I could obtain them, the documents bearing on these movements, I do not find the subject mentioned. But the disorder not being recognized, is no proof of its not having existed; for, when we reflect how almost entirely the accurate knowledge of diseases of the heart is the knowledge of our times, we can readily understand how difficult or impossible it may have been to have distinguished the less marked groups.

That the affection about to be described is not confined to troops engaged in actual warfare, may be judged by a statement of Coche,* that soldiers kept long under drill are liable to functional derangement of the heart with palpitation; and, by various allusions and accounts, published of late years in Great Britain—prominent among which I may refer to an able lecture by Dr. Maclean, reported in the *British Medical Journal* of February 1867, in which the term irritable heart has been adopted. But, to this day, nowhere, whether as the result of the ordinary duties of the soldier or of actual war, has the subject, so far as I can find, been made one of careful clinical investigation. . .

GENERAL CLINICAL HISTORY

The general clinical history of many of the cases was this:

A man who had been for some months or longer in active service, would be seized with diarrhoea, annoying, yet not severe enough to keep him out of the field; or, attacked with diarrhoea or fever, he rejoined, after a short stay in hospital, his command, and again underwent the exertions of a soldier's life. He soon noticed that he could not bear them as formerly; he got out of breath, could not keep up with his comrades, was annoyed with dizziness and palpitation, and with pain in the chest; his accoutrements oppressed him, and all this though he appeared well and healthy. Seeking advice from the surgeon of the regiment, it was decided that he was unfit for duty, and he

* De l'Opération Médicale du Recrutement.

was sent to a hospital, where his persistently quick acting heart confirmed his story, though he looked like a man in sound condition. Any digestive disturbances which might have existed gradually passed away, but the irritability of the heart remained, and only very slowly did the excited organ return to its natural condition. Or it failed to do so, notwithstanding the use of remedies which control the circulation; thus the case might go on for a long time, and the patient, after having been the round of hospitals, would be discharged, or, as unfit for active duty, placed in the Invalid Corps.

This may be stated to be a general summary of a considerable number of cases. But there were many others originating more suddenly, or without previous digestive disorder, presenting also marked disturbance or irregularity of the circulation, and having also the pain in the cardiac region well developed. I shall cite a few cases of irritable heart by way of illustrating these remarks.

CASE 261. *Irritable Heart, Previous Marked Diarrhoea; Amelioration Only of Symptoms.* William C., private, 140th New York Volunteers, twenty-one years of age, single and a farmer before he volunteered. He enlisted August 27th, 1862, had diarrhoea for about three months, and subsequently, while on a march from Harper's Ferry to Fredericksburg had his attention drawn to his heart by attacks of palpitation, pain in the cardiac region, and difficulty in breathing at night. He remained, however, on duty, though not of very hard kind, until December 24th, 1862, when in consequence of a severe cold which resulted in loss of voice, he was ordered from the front. Transferred from hospital to hospital, he was sent in June, 1863, to the U.S.A. Hospital, at Turner's Lane, where I examined his case. This note expresses his condition at the time:

"Height 5 feet 6 inches; weight 145 pounds; measurement around chest, 1 inch below nipple, 35 inches; appearance that of fair health; gums rather spongy, says that they bled easily while in the field, and he thinks he had a slight attack of scurvy; appetite good; bowels regular; respiration 24 in the minute; pulse 122; impulse of heart extended, and very jerky; first sound decidedly deficient; second sound distinct; percussion dulness not increased; capillary circulation defective; hands bluish. On lying down, pulse becomes fuller, and is reduced to 98, and after a few minutes, to 90; on rising, after lying for some time, it only very gradually regains its previous velocity. He is still aphonic, probably from catarrhal laryngitis; was etherized before I saw him, but without effect on voice. He has had lately about two nocturnal discharges a week, which has been the case with him for years, excepting when in the field and suffering from diarrhoea, when he was free from them. Has occasionally spells of dizziness."

He took, for a time, the tincture of gelsemium, but with little effect; veratrum viride, five drops of the tincture three times daily, and subsequently six drops daily, had a much better action. It reduced the pulse to 84, without materially altering the jerky character of the cardiac beat, and it had to be discontinued on account of the nausea. It was then given occasionally, while oxide of zinc, followed by strychnia, was prescribed. This, too, produced little permanent effect. November 16, he returned from a furlough, apparently in excellent health, but with an impulse of 98, and still suffering from palpitations, especially at night. He was now placed on digitaline granules, and, as it was evident that he would not be fit for active duty for a very long time, he was detailed as orderly. Under Morson's digitaline, $^1/_{60}$th of a grain three times daily, the action of the heart improved considerably. Yet when he was recommended in May, 1864, for the veteran reserve corps, he still had some cardiac pain and occasional palpitations. These, however, scarcely occurred excepting on strong exertion. It may be added that on the previous 1st of September the man regained his voice after a violent coughing spell.

CASE 87. *Irritable Heart, Chiefly from Hard Service; Recovery.* Wm. Henry H., private, 68th Pennsylvania Volunteers, admitted into the Turner's Lane Hospital in Philadelphia, November 2d, 1863, having just returned from a furlough. He enlisted in August, 1862, at the time in good health, though he had suffered occasionally from rheumatism. He did a great deal of hard duty with his regiment. Some time before the battle of Fredericksburg, he had an attack of diarrhoea; after the battle, he was seized with lancinating pains in the cardiac region, so intense that he was obliged to throw himself down upon the ground, and with palpitation. These symptoms frequently returned while on the march, were attended with dimness of vision and giddiness, and obliged him often to fall out from his company and ride in the ambulance. Yet he remained with his regiment until July 4th, 1863, when he was wounded at the battle of Gettysburg.

The wound healed in about one month; but the cardiac symptoms became worse, and violent palpitations ensued upon the slightest exertion, sometimes also whilst in bed, obliging him to rise. There was soreness in the cardiac region, and a constant dull pain. The impulse was extended, slightly jerky, 96, and of irregular rhythm, some beats following each other in rapid succession; the first sound was feeble, the second very distinct. The man did not look sick. Height 5 feet 7 inches; measured 31 inches around the chest 1 inch below the nipple; he did not smoke; chewed tobacco in moderation.

The patient did not improve under aconite; but under digitalis the impulse became quiet and

78, and on March 23d, having previously done duty as orderly, he was detailed on police duty, and his treatment stopped. The heart continuing to act regularly, he returned to his regiment May 3d, 1864.

These cases represent the cardiac malady most commonly encountered among soldiers. But side by side in the ward I soon noticed cases of hypertrophy of the heart, such as one meets with in civil practice; cases with all the forcible action of an increased organ, with its physical signs, its usual symptoms, often with a comparatively slow and laboured action; cases, therefore, wholly unlike the persistent excitement of the rapidly-beating irritable organ. Holding at the time the common belief that functional and organic affections are widely separate, I failed at first to seize the fact that the apparently dissimilar states were in reality one, or rather, that one grew out of the other. But as patients multiplied I began to trace the connection; and observation showed me what I trust to demonstrate in this paper, the links connecting the disorders. . .

SYMPTOMS

Having indicated the general history of the malady, let us look in detail at the symptoms, taking for analysis merely the cases which were really of functional kind, or at least did not present decided organic change. And in the whole examination to follow, the remarks apply to this class of cases, unless the contrary is distinctly stated. . .

Palpitation: Both the severity and frequency of the palpitations differed considerably in individual cases. In some the attacks lasted several hours, and were attended with increased pain in the cardiac region, and under the left shoulder. They were often accompanied by a great deal of distress, and were really painful. They occurred at all times of the day and night, varying in frequency from one to five or six attacks, or more, in the twenty-four hours. Yet there were cases that did not have them for days at a time. The seizures were, of course, most readily excited by exertion, and might be then so violent that the patient would fall to the ground insensible (Case 119). This happened to some on the march (Cases 8 and 45), or field of battle; or they fell in the ranks, and were taken prisoner (Book V., p. 45, and *ibid.* p. 56). But attacks also occurred when the patient was quietly in bed, disturbing his rest, or waking him up (Case 116); and some reported that they were worse at night (Cases 64 and 65), and early morning (Cases 111 and 230). They were very variously, sometimes whimsically described. The rapid action was often commented on; but a "slow, hard" beat of the heart was also spoken of (Case 202); and one soldier (Book V., p. 45) likened the cardiac derangement to the "fluttering of a chicken, when taken by the legs". . .

Cardiac Pain: Pain was an almost constant symptom. I cannot recall a single well-marked instance of the complaint in which it was wholly absent; and often it was the first sign of disorder noticed by the patient. It was generally described as occurring in paroxysms, and as sharp and lancinating; a few likened it to a burning sensation (Case 111), or spoke of it as tearing (Case 122), or as burning at times, and at others cutting; or as a "dull sullen" pain, becoming at times acute (Case 69). In some cases no other pain happened than what occurred in these sharp attacks (as in Case 91), or a mere feeling of uneasiness in the region of the heart existed; but in the large majority there was a substratum, as it were, of discomfort, or of dull heavy pain. In exceptional cases the pain was altogether of this character. . .

The chief seat of the pain was the lower part of the praecordia, particularly near the apex. But it was not always limited to the region of the heart. It was spoken of as shooting to the left axilla, as passing down the left arm (Case 111), which then felt numb; as being present under the left scapula (Case 239); and as radiating from over the heart in all directions (Case 240). The pain was associated with sensitiveness in the cardiac region, and this hyperaesthesia was apt to be increased after attacks of palpitation. In cases which ended in recovery, both pain and tenderness gradually left. . .

Pulse: The pulse was mostly noted to be very rapid, varying from 100 to 140. In character it was small, and easily compressible; it might or might not exhibit the abrupt or jerking character, which, as we shall presently see, is one of the chief peculiarities of the cardiac impulse, and this might have a certain amount of force which the pulse would lack. In some cases it was under 90, and was then apt to be fuller; these were, for the most part, the cases passing into cardiac hypertrophy. The pulse exhibits under any circumstances great variations; and especially in a case

following an injury to the spine from a falling tree (Cases 232) it changed about between 76 to 120, little influenced by any remedy employed. Slight irregularities in the succession of its beats, and, indeed, in the general rhythm, are very common. The pulse is always and rapidly influenced by position. . .

In the preceding remarks the pulse has been treated of when no palpitations existed at the time. These heightened it. But even when palpitation was not present, the beat at the wrist reached occasionally an extraordinary rapidity. Thus, in one case (Case 303), it was irregular, and seemed like a wave, slightly jerking and with intermissions; counted as accurately as possible, it was not under 192. Gradually, by rest and digitalis, it was reduced to 110. . . The hands were often bluish, and other portions of the skin mottled, and rendered pale on pressure; in truth, the whole capillary circulation was often palpably defective.

Respiration: Shortness of breath, or rather oppression on exertion, was constantly complained of, and was a prominent symptom during attacks of palpitation. When the heart was acting in its usual way, a certain amount of embarrassment in breathing was also commonly spoken of, and was at times so severe that the patient was obliged to sit up in bed. Yet, notwithstanding all the signs of dyspnoea, it was astonishing that the respiration was so little hurried. And, as a general rule, it may be stated that this curious disorder presents the anomalous condition that increased action of the heart does not give rise to increased frequency of breathing; we find in it a peculiar pulse respiration ratio, and one just the reverse from that of pneumonia. . .

Nervous Disorders: These manifested themselves chiefly by headache, giddiness, disturbed sleep; and were symptoms which, though common, were not so constant as those already described. The headache was not apt to be persistent, but to occur in spells, and was generally of a dull, heavy character. It was more particularly noticed after severe attacks of palpitation; and might (as in Case 149) be associated with giddiness, and with increased heat and redness of face. . .

PHYSICAL SIGNS

The *impulse* is almost always extended, yet not correspondingly forcible; rather, it is quick, and abrupt or jerky. When the hand is applied to the praecordial region, it may note the quick impulse happening in a regular manner, or it takes cognizance of the irregularity of rhythm of the irritable organ. Further, it may at times perceive the two sounds of the heart; feel them as it were (as in Case in Book V., p. 33). On listening to the heart, the first sound is found to be lacking in volume, feeble or short and valvular, and just like the second sound (Cases 112 and 136); and the valvular character of the first sound may be best appreciated a little to the left of the impulse (Case 285). As recovery ensues, the first sound gradually regains its usual character, and it may do this, although when it originally came under observation it was almost extinct (Case 170). The second sound of the heart is generally increased, and always very distinct; I met with but one instance (Case 147) in which it was the reverse. The sounds of the heart are freely transmitted beyond the cardiac region; the second sound may be heard very clearly defined over the carotid (as in Case 141). Sometimes the sounds of the heart are split. . .

Murmurs obscuring or replacing the cardiac sounds are not as a rule present; yet they are met with, and particularly is that form of murmur, systolic, chiefly above the apex, and not connected with venous hum or other signs of anaemia, which I have described (see this journal, July, 1869) as significant of functional valvular disorder. . .

COURSE OF THE DISORDER

Having discussed the symptoms and physical signs, it will be useful to inquire into the course of the malady. This mostly either gradually subsides, or it passes by degrees into cardiac enlargement.

When the disorder yields, the heart becomes less and less irritable, exercise no longer affects it so much, the cardiac pain and soreness disappear, and finally the patient is again able to bear fatigue and undergo exertion; or in other instances, he is well as long as he is not too active, but his heart is always liable to be more disturbed by undue exertion or by excitement than the heart of a healthy person is. I shall give some illustrative cases, selecting partly those that returned to their regiments, but chiefly those that I had opportunities of observing after they left the service. . .

CASE 48. *Irritable Heart; Permanent Recovery; Does Duty in the Veteran Reserve; Patient Seen Very Recently:* Joseph W., enlisted in the 12th New Jersey

Infantry in 1862, when 17 years of age. Was not strong, and picket duty and marching soon told heavily on him; he commenced to suffer with dizziness, with cardiac pain, shortness of breath, and palpitation. The long march from Falmouth, Virginia, to Gettysburg, broke him down completely; on the second day of the march he threw away his knapsack and extra clothing, and could even then scarcely keep up with the regiment. He was soon afterwards sent to a hospital in Philadelphia, where I saw him July 13, 1863. The pulse was 104, very feeble; the impulse jerky, and felt in two intercostal spaces; the second sound was somewhat exaggerated, the first only moderately distinct. The man's weight was 128 pounds; height 5 feet 5 inches; measurement of chest 27½ inches. He improved under a treatment of digitalis, veratrum viride, and iron, given singly, and sometimes suspended to treat troublesome attacks of cough, to which he was subject. But as he was a weakly-looking lad he was detained in the hospital, doing light duty, and March 13th he was recommended for the Veteran Reserve, 1st battalion, as his physique did not warrant his being sent into the field. But the heart difficulty had yielded, the impulse had lost its jerk, and the first sound was of good volume. His first duty before he joined the Veteran Reserve battalion was guard duty in Philadelphia, and I had an opportunity of examining him June 29, 1864. The impulse was 70, regular; he had no longer palpitation, and only occasionally cardiac pain.

Early in November of 1870, just as this paper was going into the hands of the printer, a tall, broad-chested, fine-looking young man came into my office, in whom at first I did not recognize the puny soldier of 1864. He told me that he served his term out, of about one year, in the Veteran Reserve, first at Washington, and then for seven months in the interior of Ohio. Here he was on detached service, on the provost guard, was mounted, lived very constantly in the open air, and did sometimes hard riding. On one occasion he ran his horse for nine miles at full speed in the pursuit of a prisoner, but neither this nor any other service brought back the cardiac disorder. In fact he was never off duty, had neither pain nor shortness of breath, and only twice an attack of palpitation, happening after a "bilious spell." He weighed 142 pounds when his term expired; and it is evident that he could then have re-enlisted for active service in the field. Since he left the Veteran Reserve has been most of the time a house-painter. Never has anything now that reminds him of his former trouble. Can go up and down stairs rapidly, or run, without being soon out of breath; weighs 127 pounds; still takes cold occasionally. The pulse is about 78; the impulse of the heart of good strength, not in the least jerky, is still felt in two intercostal spaces; the first sound is of good volume, if at all different from the normal average it is rather heavier; the second sound is not of exaggerated distinctness; the percussion dulness is normal. . .

Case 184. *Irritable Heart; Great Improvement, Yet Traces of the Disorder When Last Examined:* Nelson F., 93d New York Volunteers. In this case the derangement of the heart was first noticed after a a fever, though before he had done a good deal of hard service. The heart's action was not particularly rapid, 92 was its highest, and usually it was 80; but it was extremely irregular, and there was considerable soreness in the cardiac region. He improved much under treatment, especially under digitalis, but being, in consequence of an injury to his arm, considered unfit for duty, he was discharged. I saw him six months afterwards; he had been travelling and acting as nurse; he still had palpitation occasionally on exertion, and a slight double beat of the impulse could at times be perceived; yet for the most part, the action of the heart was regular; the pulse was 78.

Case 7. *Irritable Heart; Recovery Not Complete When Last Seen:* P. S., 82d New York Volunteers, had diarrhoea at Harrison's Landing, in August, 1862, but did not notice any cardiac trouble until in September, after the battle of Antietam. He remained, however, on duty for several months, until he received a slight wound in the shoulder. Examined on April, 1863, I noted him as having pain over the heart, and occasionally palpitation, especially after exertion; pulse of moderate volume; impulse somewhat abrupt, not extended; first sound ill developed, lacking in weight; second sound very distinct. He was placed on digitaline, and had improved considerably when, in obedience to a general order, he was sent to his regiment. January 31, 1868, he came to see me at my office. He told me that he had not been able to do duty with his regiment, and that he had been mostly on provost duty, until his time expired in June, 1864. He has been since only rarely troubled with palpitation, but much much exertion still makes him feel weak, and somewhat short of breath. Yet he can go up stairs without exciting inordinate beating of the heart, has no cardiac pain, and considers himself as well. The first sound of the heart was still short, dull, and confused; the pulse was 72, compressible, the beats not quite regular.

Here then was a case in which an all but complete recovery ensued, a slight cardiac derangement being, however, traceable for years. In the preceding case it was also discernible, though not for so long a time, and it is very likely that this ended in recovery. This happened in a man (H. K., Book V., p. 72) who was mustered out of the service at the end of the war, still having palpitations occasionally, though he had greatly improved, and who has lately told me that for two years his heart

continued to give him some trouble, yet now he is well and a hardworking carpenter.

To examine now an entirely different result of the irritable heart, a group of cases in which *the disordered function leads to organic disease.*

CASE 41. *Irritable Heart; Hypertrophy Results.* James, A. E., private, 136th New York Volunteers, enlisted September, 1862; when first seen, in June, 1863, had clearly an irritable heart, which had resulted from fever and hard duty. The attacks of palpitation were very frequent, and he could not walk across the ward without bringing one on and increasing the cardiac pain. The pulse ranged between 98 and 118, was feeble, occasionally intermitted, and the beats were of unequal strength; immediately on lying down the pulse became fuller, and fell to 72. The impulse of the heart was abrupt and extended; the first sound deficient, the second very distinct; percussion dulness was of normal extent.

This case proved very unyielding to treatment, and though the action of the heart became slower, the palpitations did not cease. Very likely the cardiac irritability was kept up by repeated attacks of cough, to which he seemed very liable. He was in April, 1864, put in the Veteran Reserve, 2d Battalion, having done duty first in charge of a ward; he served while in the Veteran Reserve on guard duty, always remaining subject to palpitation on strong exertion, and the impulse being of moderate force.

I met him in August, 1865, and though he said he was well excepting when he fatigued himself, it was evident that the heart had become hypertrophied; the impulse towards the apex was more forcible than normal, and the first sound heavier; the second sound had lost its increased distinctness; the transverse percussion dulness measured $4^1/_2$ inches. . .

All these cases . . . were cases in which the enlargement of the heart occurred after they passed from under my hands and mostly after their return to civil life. But I find among my records instances in which the change took place in spite of treatment, and while the patient was actually under observation, or had been so most of the time. Such a one was Case 225, which is described as a very decided example of irritable heart, July 18, 1864, with an abrupt impulse, beating 124 times in the minute; a short first sound. October 13 the first sound is noted as somewhat stronger; the transverse diameter of the heart is $2^3/_4$ inches; the impulse is unreduced in frequency. The man was withdrawn from my control for upwards of a month; the impulse is then stated to be more forcible, and the heart is kept much disturbed by recurring malarial outbreaks and by intemperance. May 19, 1865, when the last note is taken, the case is one of undoubted dilated hypertrophy; the first sound is rather heavy, the second less distinct; the impulse is 108, extended, somewhat forcible; the transverse diameter is 4 inches. A similar record is made in Case 236; while in others (as in Case 145), men who are not steadily under treatment, or who obtain furloughs, or are sent away in obedience to general orders, to meet exigencies, are found at first with forcible hearts and just beginning enlargement, which on different opportunities for examination is observed to have become much more developed.

In the light of these cases we can interpret others. We can understand how it happened that Case 185, a man who had been in sixteen fights, and for two years had not been off duty a day, though gradually more and more troubled with palpitation, and much distressed while carrying his knapsack on long marches—how such a man, who was often obliged to halt and sit down until the spell had passed off, but who loved the excitement of campaigning so much that he would not leave his regiment—we can well understand how it was that, giving his heart no chance for recovery, he should have presented all the signs of most marked hypertrophy. We can further understand cases sent to the hospital when this state was beginning, and in which the irritable heart was just passing into, or had just passed into, the enlarged heart . . .

DIAGNOSIS

The diagnosis of the affection has become evident from the preceding remarks, and I shall confine myself here to a few general statements, chiefly about matters that have not been explained or touched upon. And first, of the cases last discussed, and which were viewed in a state of transition to hypertrophy. It is necessary to mention that in exceptional instances they are simulated by irritable hearts, in which the first sound is heavy, and the impulse rather forcible; but the percussion dulness is not increased, and whether we view them as cases arrested at the very beginning of organic change or not, it is certain that (as in Case 77) the heart returns apparently to a perfectly natural condition. In some instances of the kind it may be necessary to watch the effect of treatment—which, generally, rather rapidly influences the disordered organ—before a positive conclusion can be reached.

As regards the examples of hypertrophy we must bear in mind that fixing the boundaries of the heart only once is not sufficient for diagnosis, for increased dulness on percussion may be temporarily caused by engorgement of the cavities with blood. Again, both with reference to cases of hypertrophy and of irritable heart, we must remember, as above explained, that blowing sounds from excitement and functional valvular disorder are very common; and must guard against confounding the cases, on account of these murmurs, with valvular disease of the heart. I may add that I have known many a man discharged the service for organic valvular disease, who presented merely the combination of phenomena here referred to. The similarity may be greatly heightened by the coexistence of dropsy, a sign I very seldom noticed in the cases of hypertrophy, still more seldom in those of irritable heart; but which does happen in either, and when coexisting with a cardiac murmur may perplex the most skilful diagnostician. In Case 187 this combination was present, but all the signs disappeared and the man recovered. The dropsy of the irritable heart is limited to the lower extremity, and is apt to be very transitory.

Dilatation of the heart I encountered only very rarely. Where it existed it might have been confounded with irritable heart; but the extent of the percussion dulness, and the marked tendency to dropsical effusions were very significant features. Anaemic hearts are distinguished from irritable hearts by the history, by the murmurs at the base, the venous hum, the aspect of the patient, and the absence of cardiac pain. Occasionally the two affections are combined, but I have left out these instances in the analysis on which this paper is based.

It would seem scarcely necessary to speak of the differential diagnosis between irritable heart and phthisis. Yet they may be mistaken. Slight irritative coughs or attacks of bronchitis are not uncommon, perhaps more common than in persons whose circulation is not disordered, and with the disposition to shortness of breath and the rapid pulse may well mislead . . .

Lastly, it is impossible to discuss any malady to which soldiers are liable without discussing its being feigned. And a malingerer, as is well known, may keep up a rapid action of the heart by a tight bandage around the upper part of the abdomen and lower part of the chest. But, excepting if this be done, the imitation is a very clumsy one. The impostor knows nothing of the character of the cardiac pain. Further, making him lie down after undressing causes the heart to return to its natural beat; and then on his resuming the erect position, or walking around quietly, it will not, as an irritable heart does, regain its former frequency or irregular rhythm. And the peculiar physical signs of the irritable organ, and its persistently rapid action when examined under any circumstances save when the patient is in the recumbent posture, are traits which cannot be copied . . .

CAUSES

Occupation appears without influence on the production of the malady. Painter, butcher, blacksmith, carpenter, the city-bred man who had left his desk in the counting-house, the farmer fresh from tilling the fields, were all fully represented in the long list of sufferers.

When now we take a comprehensive view of the general causes of the malady, we find quick and long marches, heavy work, producing the affection, or even slight exertion in those whose constitution has been impaired by insufficient or indigestible food, or whose strength has suffered, or condition of the heart been disturbed by diarrhoea or fever. We find it most readily developed in those previously weak and unaccustomed to fatigue, or subject to readily-quickened circulation. We find it kept up by irksome equipments, and other causes, but not generated by them.

But in looking further, and in endeavouring to explain the *nature of the malady*, there is room for much doubt and difference of opinion. It seems to me the most likely that the heart has become irritable, from its over-action and frequent excitement, and that disordered innervation keeps it so. But our knowledge of the nerves of the heart, and their special functions, is as yet too incomplete, to say which nerves lie at the root of the disturbance. . . As evidence how the sympathetic system participates, might also be cited the obvious disturbance of the capillary circulation and the perspirations. . .

In bringing this inquiry to an end, I may be permitted to point out what I believe to be its chief interest and value. To the medical officer it may be of service as investigating a form of cardiac disorder which every severe or protracted campaign is sure to develop. And from a military point of view, further, it

enforces the lessons, how important it is not to send back soldiers just convalescent from fevers or other acute maladies, too soon to active work; it suggests that their equipments be such as will not unnecessarily constrict, and thus retard or prevent recovery; that recruits, especially very young ones, be as far as practicable exercised and trained in marches and accustomed to fatigue before they are called upon to undergo the wear and tear of actual warfare; and it exhibits some of the dangers incident to the rapid and incessant manoeuvring of troops. True, on a movement executed on the double-quick may depend the issue of a battle, a forced march may determine the fate of a nation; and the time can never come when purely physical considerations can forbid, either one or the other, or dictate how often they may be ordered. But every commander should be made aware that in so using his men he is rendering some unfit for further duty, impairing others, and thus be led to count the cost of the frequent use of such active movements as carefully as he would the holding of a particular part of a line or the assault on another.

But the chief value of this inquiry is after all to the practitioner of medicine. It traces, I venture to hope that I may say establishes, the connection between functional derangement and organic change, and examines the intermediate steps. And it is a contribution, based on trials made on a very extensive scale, towards the accurate knowledge of the action of remedies on the heart; showing, among other points, how a remedy may especially influence one of the elements of disorder without affecting the others. . .

* * *

Comments

Da Costa's paper is an impressive example of nineteenth century clinical research, conducted entirely by simple methods of history taking and physical examination without the assistance of the laboratory. The author was aided by a wise policy of the War Department, which concentrated cases of irritable heart in the hospital at Turner's Lane at Philadelphia under Da Costa's care. This favored the rapid accumulation of data and the synthesis of the clinical picture. A similar method had been in use in the hospitals of Paris and was extremely helpful if not essential to the work of Laennec and his great contemporaries.

In the brief retrospective comments which occur in the second paragraph of his article Da Costa mentions a few statements which suggest that cases similar to his own were observed during the Crimean War but apparently were not subjected to detailed study. He also makes the significant and correct comment that the accurate knowledge of heart disease was almost entirely the product of his own era.

The clinical picture which he portrays consists of palpitation, pain near the apex of the heart, shortness of breath, dizziness and sweating. Often the patients had had infections, especially infections of the gastrointestinal tract. The palpitation was usually paroxysmal and was often exertional. The heart sounds showed minor modifications and varied arrhythmias. It was characteristic for the pulse rate to be greatly reduced by recumbency and it might decline during intercurrent infection. Respiration was often oppressive but not accelerated. Sweating was frequent. The hands were sometimes cyanotic, the skin mottled.

Da Costa recognized that the value of his case studies would be improved by repeated observation at long intervals. He contrived to follow up some of his patients for periods as long as seven years. This device, which we erroneously tend to regard as a recent invention, permitted him to recognize the fact that many of his patients recovered. He believed—and this conclusion is important—that in some of those who did not lose their symptoms there was a tendency for cardiac hypertrophy to develop.

Among the causes to which Da Costa attributed etiologic importance the most common was infection, especially infection of the gastrointestinal tract. In the present state of knowledge it is doubtful that this attribution can stand against critical analysis, since gastrointestinal infection was extremely common during the Civil War. We are further warranted in assuming that some of Da Costa's patients may have had rheumatic fever; others may have had hyperthyroidism, tuberculosis or chronic malaria. It is highly probable that some had scurvy, and we cannot exclude the possibility that this disease, a rarity today, may exert an unrecognized influence on the cardiovascular system. If all these are subtracted there would still remain a miscellaneous group, vaguely designated as idiopathic, for which the sophisticated cardiology of the twentieth century has as yet no completely satisfactory explanation.

Synchronization and Accrochage in the Presence of Incomplete Heart Block*

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THE SUBJECT of synchronization and accrochage, a phenomenon first described by Segers[1,2] has been reviewed recently by Marriott.[3] Briefly, this phenomenon consists of synchronous contractions of the atria and ventricles in spite of the presence of complete heart block; in other words, these chambers, although completely independent and responding to their own pacemakers, "walk for a while in step."[3] This "hook-up" may be brief (accrochage) or last for longer intervals (synchronization).

It is my purpose to report herein the electrocardiograms of a patient whose records may represent another example of this rare phenomenon.

CASE REPORT

A twenty-four year old man was admitted to the hospital for the second time on June 25, 1958, in a state of acute pulmonary edema. On his first admission to the hospital, six months previously, he was diagnosed as suffering from rheumatic heart disease, mitral stenosis and aortic insufficiency. He was digitalized and discharged on a maintenance dose of 0.25 mg. digoxin daily. Despite therapy with digitalis and administration of mercurial diuretics, his condition deteriorated steadily until the present admission.

On admission the patient was markedly dyspneic and slightly cyanotic. The heart rate was 130 per minute and regular. The blood pressure was 140/60 mm. Hg. The jugular veins were markedly engorged, rales were heard at both bases and the liver was markedly enlarged and tender. Peripheral edema or ascites were not present. X-ray examination of the chest showed engorged lung fields and hili, moderate cardiac enlargement, elongation of both cardiac borders and bulging of the main pulmonary artery.

The *electrocardiogram*, taken on admission, was interpreted as showing "mid-nodal tachycardia" (Fig. 1). The patient received 0.75 mg. digoxin intravenously on the day of admission and again on the following day. Medication was then stopped because signs of overdigitalization in the form of nausea and vomiting appeared. The patient's acute distress improved but the subsequent clinical course suggested the presence of bacterial endocarditis, which was confirmed by positive blood cultures. He is now being treated for this condition.

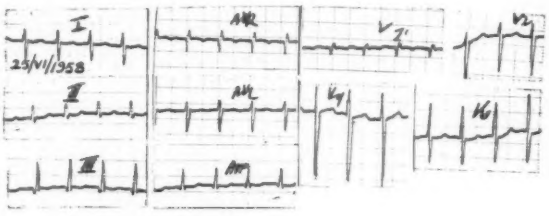

FIG. 1. Electrocardiogram on admission (see text).

The salient electrocardiographic features were as follows: *June 25, 1958 (Fig. 1)*: Initially interpreted as "mid-nodal tachycardia," later considered first degree heart block and probable auriculoventricular synchronization (see section on findings and comments). *June 25, 1958 (Fig. 2)*: A, B following 0.5 mg. digoxin and C, D following 0.75 mg. digoxin intravenously. This is described in detail later. *June 27, 1958 (Fig. 2E)*: Taken following withdrawal of digitalis. First degree heart block, P-R interval = 0.44 second. *June 29, 1958 (Fig. 2F)*: First degree heart block improved, P-R interval = 0.32 second. *July 1, 1958:* P-R interval = 0.20 second. Mitral P waves. No sign of ventricular hypertrophy. The electrocardiogram has since remained practically unchanged.

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Description of the Electrocardiographic Findings and Comments

The occasional appearance of P waves of sinus polarity emerging from under the QRS in subsequent tracings (Fig. 2, A, B, C, D), dismisses readily the first assumption of "mid-nodal rhythm." A plausible explanation of the tracings is as follows:

At the beginning of Figure 2A (see diagram on top of A), second degree heart block with the Wenckebach phenomenon is present: the first P is not conducted, the respective P-R intervals of the second and third auricular beats are 0.50 and 0.72 second, the fourth auricular beat is not conducted, the fifth P-R interval is 0.52 second. In all likelihood, the first and fourth P waves, although not reaching the ventricles, do partially penetrate the A-V node (concealed conduction[4]). This may explain the prolonged P-R interval of the second and fifth auricular beats despite the preceding pause. From the fifth to the seventeenth P wave, the P-R interval becomes practically fixed, prolonged to proportions of first degree heart block, and, with slight fluctuations, it equals the R-R interval (P-R = 0.56 ± 0.04); each P wave merges with the QRS or appears occasionally before it (P_7, P_{12}, P_{14}) or after it (P_9, P_{11}). From P_5, to P_{17}, therefore, each P wave belongs to the ventricular complex following the one with which it merges. From the seventeenth to the twentieth P wave, second degree heart block with the Wenckebach phenomenon is again present, the respective P-R intervals being 0.52, 0.60, 0.62 second, and the twentieth P not conducted. From then on, every other auricular impulse is transmitted to the ventricles with marked delay, this being again the probable result of "concealed conduction" into the A-V node of the blocked auricular beats.

In Figure 2, B and C, a similar mechanism is present with the P-R interval becoming even longer than R-R interval toward the middle of the tracing. Here, for a few beats, the sequence mimics normally conducted sinus beats, although it should be stressed that the auricular impulse is not transmitted to the adjoining ventricular complex but to the following one with a P-R interval prolonged to 0.60 second or more. In other words, in those beats, the P waves "skip" over a ventricular complex ("skipped P waves").[5] Toward the end of Figure 2, B and C, as in A, every other atrial contraction is transmitted to the ventricles with considerable delay,

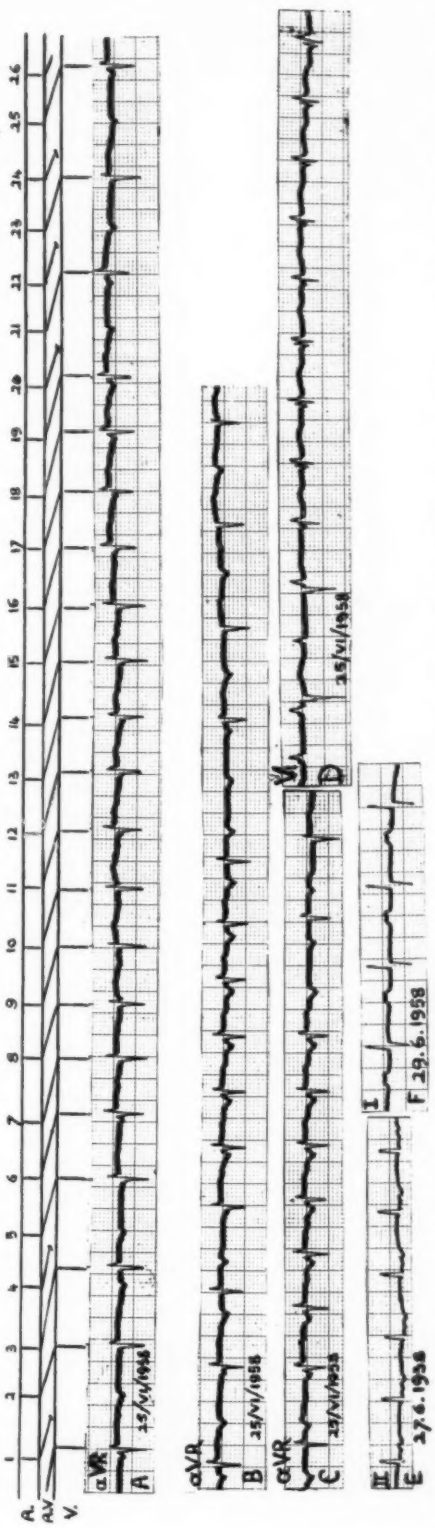

FIG. 2. The convention in the diagram above (A) is as follows: The vertical lines at the level of A indicate atrial activation and the numbers above them their order of appearance. The lines at the level of V indicate ventricular activation. The oblique lines at the level of A-V indicate conduction from the atria to the ventricles while the short lines at right angles to them indicate stoppage of the impulse. (A), (B), (C) are parts of lead aVR, (D) is part of lead V_1, all taken on June 25, 1958. (E) is part of lead II, taken on June 27, 1958. (F) is part of lead I taken on June 29, 1958. A, B, C, D were taken during therapy with digitalis; E, F after withdrawing digitalis (see text for details). In order to clarify the tracings, some have been retouched.

the R wave of the second and third last ventricular complex in Figure 2B being dwarfed by the superimposed negative P wave. The P wave therefore appears sometimes before, sometimes after the QRS, or sometimes merges with it. This wandering of the P wave around the QRS is also well seen in Figure 2D.

The assumption of marked first degree heart block receives further support from the tracings in Figure 2, E and F which show gradual normalization of the P-R interval upon withdrawing digitalis. (P-R = 0.44 second in E, 0.32 second in F.) Thus a remarkable feature of this tracing is the fact that short episodes of second degree heart block are followed each time by longer episodes of first degree heart block, the P-R interval of which has a tendency to equal the R-R interval, the P wave when approaching the QRS remaining close to or buried in this QRS. This feature is probably not accidental as in many tracings taken that day it repeated itself over and over again.

Mechanism of Synchronization: As in the previously published cases,[2,3] the mechanism of synchronization[1] can be invoked here to explain this peculiarity. The impression gained is that once P approaches the QRS to about 0.10 to 0.12 second, the ventricular rate accelerates to match the auricular rate and these chambers remain "hooked up" for seconds or minutes, mimicking at times "mid-nodal" rhythm (Fig. 1) or even sinus tachycardia (Fig. 2, B and C).

This explanation invokes synchronization of the special type suggested by Marriott,[3] i.e., the atrial impulse being hooked up with the ventricular impulse of the preceding cardiac cycle (middle of Fig. 2, A, B and C) or two to one synchronization as described by Segers[1] (end of Fig. 2, A and B).

An alternate and perhaps simpler explanation, also based on the concept of synchronization, would be that, for example in Figure 2A, synchronization starts with the sixth P wave onward, each P hooking up the QRS in which it merges, instead of hooking the following QRS.

The fact that, both in Marriott's case[3] and in our own, synchronization appeared during therapy with digitalis raises the question as to a possible favoring effect of this drug in the development of this phenomenon.

Finally, it should be stressed that the possibility of atrioventricular synchronization should be included in the differential diagnosis of the paroxysmal tachycardias.

Summary

An electrocardiogram presenting first and second degree A-V block, "concealed conduction" and "skipped P waves," suggesting the presence of auriculoventricular synchronization, is described.

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Case Reports

The Murmur of Mitral Stenosis; Modification by A-V Dissociation*

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THE purpose of this report is to describe some interesting modifications of the auscultatory phenomenon resulting from A-V dissociation, in a patient with mitral stenosis.

CASE REPORT

D. W., a thirty-seven year old Negro woman, was admitted to the Philadelphia General Hospital because of easy fatiguability, palpitation and painful swelling of the fingers and ankles of two weeks' duration.

Past history revealed rheumatic fever at the age of sixteen years, a normal pregnancy at twenty-four and a transient attack of pain in the left side of the chest, palpitation and hemoptysis at thirty-three years. A chest roentgenogram taken at the time of employment eighteen months prior to admission showed cardiac enlargement.

Physical Examination: The patient was a slightly obese woman who did not appear acutely ill. The pulse was 80 per minute, rhythm was irregular, the blood pressure 110/70 mm. Hg, respiration 20 per minute and temperature 99°F. No objective joint manifestations were observed. The jugular veins were not abnormally distended. The lung fields were clear. The heart was slightly enlarged to the left by percussion. A diastolic thrill was present at the apex. A regular cardiac rhythm was interrupted by periods of irregularity. At the apex, during the long cycles, an accentuated first heart sound, an opening snap and a pandiastolic rumble were heard. In addition, during the short cardiac cycles, a loud presystolic rumble was present. A soft early systolic "flow" murmur was heard at the base. The liver was normal in size and no peripheral edema was noted.

Laboratory Data: Urinalysis and hematologic examination were normal. Blood cultures were sterile. The sedimentation rate (Wentrobe) was 40 mm. in one hour. The antihyaluronidase titer was greater than 1,024 and the antistreptolysin titer was 512. Serum glutamic oxaloacetic transaminase was 48 units. The circulation time, arm to tongue, was 12 seconds, arm to lung, 4 seconds. Chest roentgenograms showed straightening of the left border of the heart and an enlarged left atrium.

Clinical Diagnosis: The clinical diagnosis was rheumatic heart disease, mitral stenosis, acute rheumatic carditis, A-V dissociation.

Course: The arthralgia responded to salicylate therapy. The sedimentation rate, antistreptolysin and antihyaluronidase titers remained moderately elevated after a month, at which time the patient was discharged to convalesce at home.

GRAPHIC TRACINGS

Electrocardiograms (Fig. 1): The configuration of the QRS and T were normal, but the P waves were notched in leads I, II, aVF and V_2 to V_6. There was sinus arrhythmia and nodal escapes after long P-P intervals leading to isorhythmic A-V dissociation. In some beats, the nodal pacemaker completely controlled the heart (retrograde P waves labeled P′), while in others there were fusion beats in the atrium (labeled P″). This arrhythmia disappeared after the second day, and upon discharge from the hospital one month later, sinus bradycardia was present.

Phonocardiograms (Figs. 2, 3 and 4): The first

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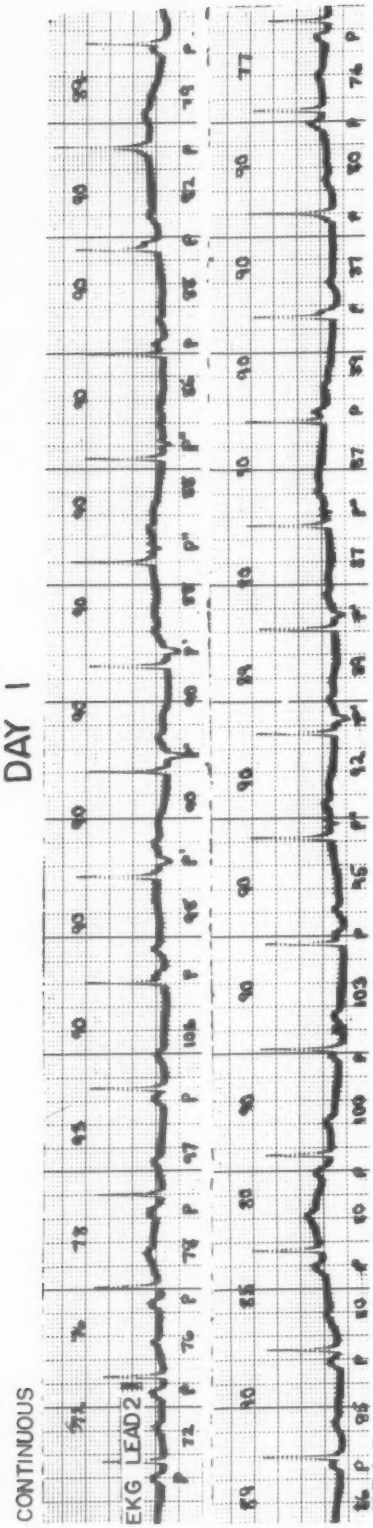

FIG. 1. A continuous tracing of lead II recorded on admission. The numbers above the electrocardiogram denote R-R intervals, while those below it, the P-P intervals in milliseconds. P = sinus P waves; P′ = retrograde nodal P waves; P″ = fusion P waves. The tracing shows sinus arrhythmia, nodal escape, isorhythmic A-V dissocation and lower nodal rhythm.

heart sound was delayed. At the apex, an opening snap followed by a diastolic rumble was recorded. A loud presystolic rumble was recorded only when the P wave was conducted and not during periods of A-V dissociation when the P wave overtook the QRS complex or during lower nodal rhythm. On succeeding days, as the rhythm returned to normal sinus, the presystolic rumble was present with every cardiac cycle. The intensity of the diastolic rumble decreased as cardiac rate slowed. The opening snap was loudest at the third interspace to the left of the sternum. The Valsalva maneuver caused the physiologic split second sound to fuse and the 2-OS distance to lengthen or remain unchanged. Following the termination of the maneuver with inspiration, the physiologic split second sound widened and the 2-OS distance shortened or remained the same. The Valsalva maneuver decreased the intensity, while inspiration increased the intensity of the pulmonary systolic murmur.

Jugular Tracing (*Fig. 5*): This showed a normal pattern during sinus rhythm. However, during A-V dissociation the *a* wave merged with the *c* wave. When the *a* wave occurred after the first heart sound, no presystolic rumble occurred.

Carotid Tracing: A normal contour was recorded.

Apex Cardiogram: The opening snap was recorded between the wave responsible for atrioventricular valve closure and that for rapid ventricular filling.

COMMENT

This case clearly shows, as is generally accepted, that atrial ejection of blood into the ventricle prior to ventricular systole is responsible for the presystolic rumble in mitral stenosis. The presence of A-V dissociation affords an opportunity to observe graphically the variations in the auscultatory phenomenon.

The Valsalva maneuver is of value in separating the opening snap from a physiologic split second sound. Normally, the aortic valve closure component of the second sound precedes the pulmonic valve closure component. The Valsalva maneuver diminishes venous return and increases the flow of blood from the lungs to the left side of the heart. Thus, left ventricular systole is prolonged and right ven-

FIG. 2. Phonocardiograms recorded at 25 mm./second on days 1, 2 and 3. (All phonocardiograms are logarithmic tracings.) 1 = first heart sound; 2 = second heart sound; OS = opening snap; DR = diastolic rumble; PR = presystolic rumble. The opening snap occurs in every cardiac cycle. The intensity of the diastolic rumble increases with the shorter cycles. The presystolic rumble is heard only when there is a normal PR distance.

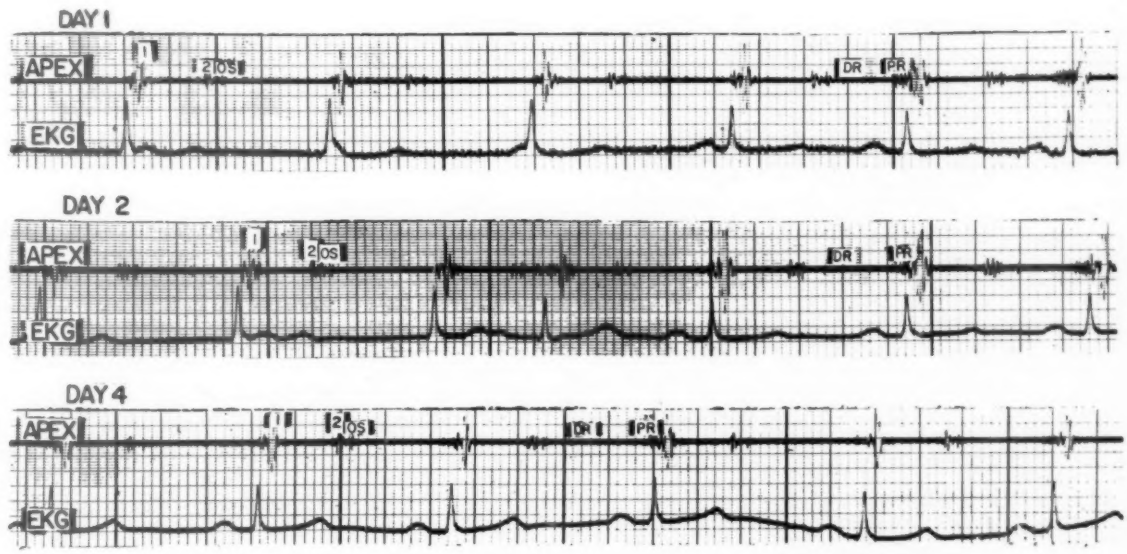

FIG. 3. Phonocardiograms recorded at 75 mm./second on days 1, 2 and 4.

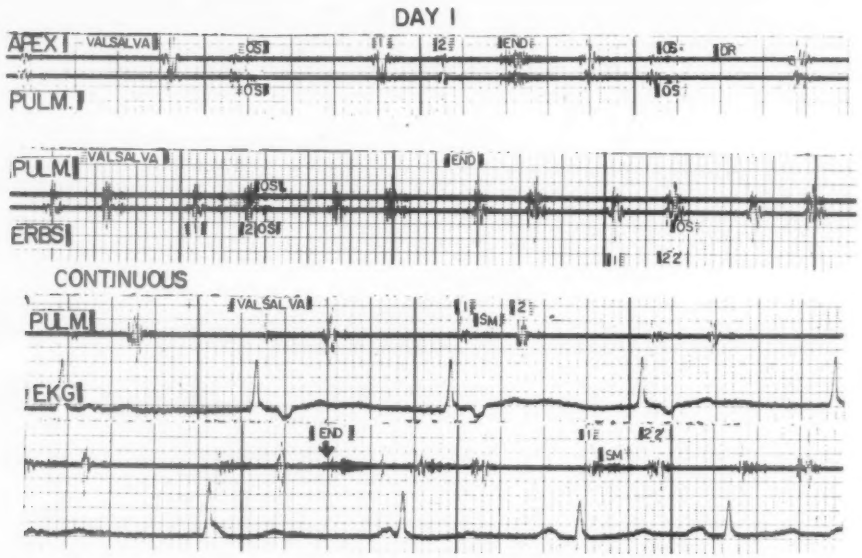

FIG. 4. Value of Valsalva maneuver in distinguishing opening snap. Phonocardiogram recorded at 75 mm./second. 1 = first heart sound; 2 = second heart sound; 2′ = pulmonic component of second heart sound; SM = systolic murmur. The Valsalva maneuver causes the physiologic split of the second sound to fuse and clearly separates the opening snap. Inspiration following the termination of this maneuver causes widening of the physiologic split second sound and merger with the opening snap. In the lower tracing of the pulmonic area, the Valsalva maneuver diminishes the intensity of the systolic murmur while inspiration increases it, indicating that it probably originates from the pulmonic valve.

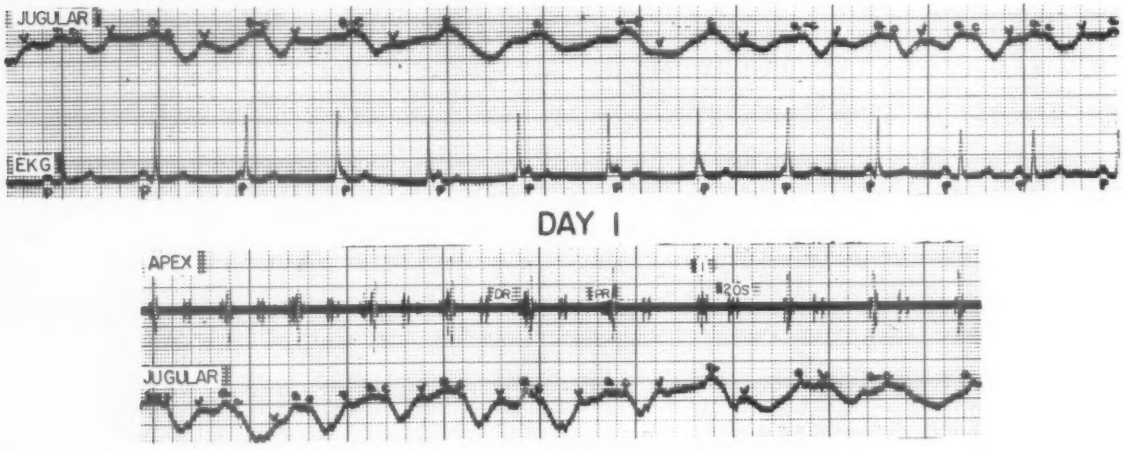

FIG. 5. Jugular pulse tracing with electrocardiogram and phonocardiogram recorded at 25 mm./second. When the *a* wave overtakes the first heart sound, no presystolic rumble is recorded.

tricular systole shortened; the two components of the second sound fuse. In a similar fashion the opening snap is delayed like the aortic component of the second sound and the 2-OS distance either remains the same or is increased. When the maneuver is terminated by inspiration, an opposite train of events takes place.

Escape-Capture Bigeminy

Bigeminal Rhythm Due to 3:1 S-A Block Associated with A-V Dissociation*

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PARSONNET et al.[1] in an electrocardiographic study described twenty-seven mechanisms of bigeminal rhythm and Perelman and Miller[2] described eleven mechanisms of bigeminy associated with atrionodal rhythm. Pseudoreciprocal type of bigeminy occurs in A-V dissociation and consists of a nodal escape beat paired with a conducted atrial beat, a P wave being sandwiched between the two ventricular complexes. The P wave in this rhythm is usually of a normal sinus contour while in true reciprocal rhythm it is of a retrograde character. Recently, Bradley and Marriott[3] suggested the term "escape-capture bigeminy" for pseudoreciprocal rhythm because it is simpler, more directly descriptive, and leaves no doubt of the underlying mechanism. Such a type of bigeminy resulting from S-A block is rare; there are only three instances[3–5] recorded in the literature, and in one other instance[6] possibility of such a rhythm has been suggested. In all four instances the bigeminal rhythm was associated with 2 : 1 S-A block. The present case with 3 : 1 S-A block has, therefore, been considered worth recording.

CASE REPORT

A forty-six year old man was seen in the outpatient department for transient spells of dizziness for the past six weeks. Physical examination revealed no abnormality except irregularity of the heart beat. There was no history of administration of digitalis. The electrocardiograms illustrated here are cuttings from a record obtained on a single occasion. The intervals recorded are measured in one hundredths of a second.

Figure 1. Lead aVL. Upper strip shows normal sinus rhythm with a rate of 78 (P-R 16; P-P 76). Lower strip shows A-V dissociation with a sinus rate of 59–62 and a nodal rate of 57–65 (P-P 96–102; R-R 92–106).

Figure 2. Lead V_1. The four strips form a continuous record. At the beginning of the first strip there are two sinus beats with a sinus rate of 83 (P-R 16; P-P 72). The sinus P wave then disappears giving rise to a sinus pause of 1,358, equal to 18 sinus cycles, before it reappears at the end of the second strip. The pause is interrupted by ten ventricular complexes at intervals of 162, 172, 155, 122, 122, 120, 120, 96, 118 and 118, respectively. The first, fourth and eighth complexes in the pause are preceded by an aberrant upright P wave at P-R interval of 12, 14 and 10, respectively, and probably represent atrial premature beats. In the fourth complex, however, the possibility that the P wave is a sinus P and is conducted at a shorter P-R interval because of the longer recovery time in the A-V junction cannot be ruled out. The other beats in the pause are nodal escapes. The last but one beat in the second strip occurs prematurely and represents ventricular capture at a P-R of 16. This beat initiates sinus rhythm, and three more sinus beats (P-R 16) occur at intervals of 76, 68 and 72, respectively. The rest of the record shows a bigeminal rhythm due to 3:1 S-A block and A-V dissociation. The first of the paired beat is an escape beat and the second is a conducted atrial beat with a P-R of 16. The P waves are low and differ slightly in contour from the sinus P waves. The P-P intervals vary between 188 and 216 ($3 \times 63 - 72$).

Figure 3A. Leads V_2 and V_3. Same type of bigeminal rhythm is seen. The P waves in these leads are also upright, showing that they are not retrograde in character.

Figure 3B. Lead V_4. The two strips are continuous. Sinus P waves are seen on the S-T segments of the first, third and fourth, and on the T wave of the fifth ventricular complexes (nodal escapes) at intervals of 200, 132 and 146, respectively, showing 3:1 or 2:1 S-A block and A-V dissociation. The second beat is an atrial premature beat with an aberrant flat P wave and a prolonged P-R of 20. The sixth ventricular complex occurs prematurely and represents a ventricular capture at a prolonged P-R of 24. This beat interrupts A-V dissociation and

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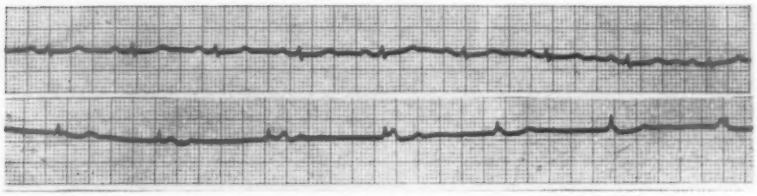

FIG. 1. Normal sinus rhythm and complete A-V dissociation.

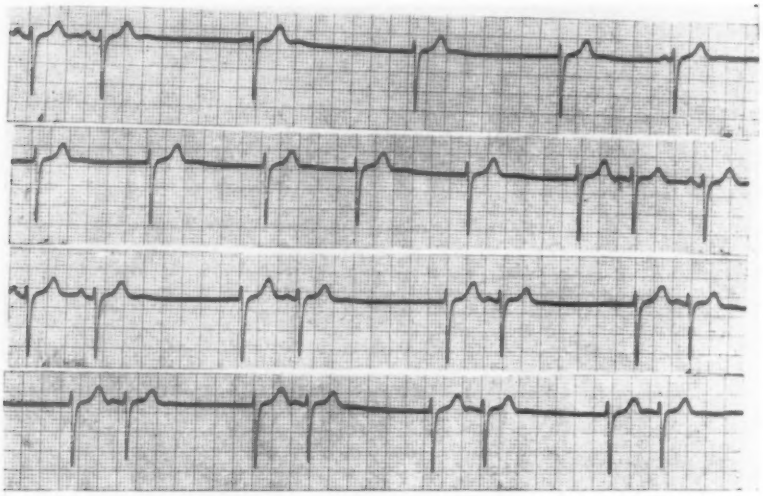

FIG. 2. Sinus pause, premature beats and nodal escapes in the pause, and escape-capture bigeminy due to 3:1 S-A block.

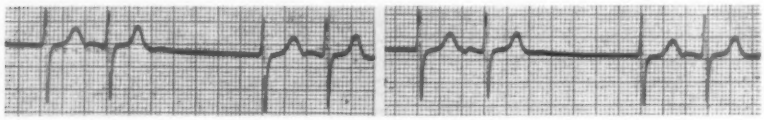

FIG. 3A. Escape-capture bigeminy.

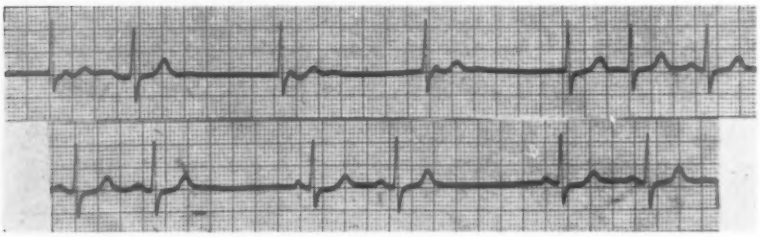

FIG. 3B. Varying S-A block with A-V dissociation, and 3:2 S-A block.

is followed by three successive sinus beats. The rest of the record shows bigeminal rhythm due to 3:2 S-A block with a sinus rate of 77–85 (P-P 70–78). The P waves in the second of the paired beats are low and differ slightly in shape from those in the first of the paired beats.

COMMENT

This electrocardiogram showed, on a single occasion, several transient disturbances of rhythm including 3 : 1 S-A block associated with incomplete A-V dissociation giving rise to escape-capture bigeminy. The conducted P waves in these couplets (Figs. 2 and 3A) are low and differ in contour from the sinus P waves. Reciprocal rhythm and pairing of escape beats with ectopic atrial beats therefore have to be considered in the differential diagnosis. In this case, in leads V_{1-3} which show the escape-capture bigeminy, the P waves

are upright and not retrograde in character, and the P-R interval of the conducted beats is the same as in the sinus beats. Again, 3 : 1 and 3 : 2 S-A block associated with A-V dissociation, and variation in the shape of the P wave in each of the two sinus beats in the bigeminy due to 3 : 2 S-A block are seen in another record (Fig. 3B). Varying shape of the P wave with gradual transition from sharp to low flat P wave is also seen clearly in the seven couplets with escape-capture bigeminal sequence (Fig. 2). Furthermore, varying shape of P waves of sinus beats is a common occurrence in S-A block, and even inverted P waves due to aberrant intraauricular conduction may occur in sinus rhythm.[6] In the record illustrated by Scherf and Schott[6] (their Fig. 86) and showing alternate upright and inverted P waves the authors have considered the possibility of pseudoreciprocal rhythm.

There is, therefore, little doubt that in the present case the escape beats are paired with sinus beats and the bigeminal rhythm is due to 3 : 1 S-A block associated with A-V dissociation. Occurrence of this rhythm was possible because of the considerable disparity between the rates, 30 and 40, respectively, of the dissociated sinus and nodal pacemakers. The arrhythmia in this case was not due to digitalis intoxication as in Bradley and Marriott's case.[3] Apparently the transient episodes of S-A block were responsible for the spells of "dizziness" in our case.

Summary

A patient with escape-capture bigeminy due to 3:1 S-A block associated with A-V dissociation is described.

Acknowledgment

Dr. L. R. Sarin, Superintendent, Sawai Man Singh Hospital kindly permitted the publication of this report.

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Book Reviews

Color Atlas and Management of Vascular Diseases, by Irving S. Wright and William T. Foley. Appleton-Century-Crofts, Inc., New York, 1959, pp. 170, $18.00.

This atlas fills a definite need as it is the first book in full color covering the peripheral vascular diseases. The photographs are taken from the authors' collection which was initiated in 1946. The book includes 192 color photographs which illustrate the lesions of ninety-four patients. The photographs are of excellent quality and each photograph has been carefully selected to illustrate an important point.

Of particular value are the "before" and "after" photographs which were taken with various forms of therapy. Because of this the reader is able to evaluate the effectiveness of the therapy employed. In general, the therapy used was conservative, although in a few cases illustrations of surgical results are demonstrated.

Most of the important peripheral vascular diseases are illustrated, including arterial diseases, venous disease, lymphedema and diseases in which vasospasm plays a major role, aneurysms, diseases of the small blood vessels and tumors of blood vessels.

These experienced authors have carefully described a large number of peripheral vascular diseases concisely yet adequately and have illustrated their examples with color photographs of the limbs, x-rays of the soft tissues including blood vessels and aortograms, pathologic microscopic specimens and therapeutic procedures. Included are useful classifications which may serve as a guide for differential diagnosis.

The book should be useful to practitioners and specialists in peripheral vascular diseases and should be used widely for undergraduate and postgraduate teaching. As there is no other book of this type in the field of peripheral vascular disease it would seem that all interested in the subject would benefit by its use.

TRAVIS WINSOR, M.D.

RECEIVED FOR REVIEW

All books received will be acknowledged in this column. Insofar as possible, as space permits, books of special interest will receive more extensive reviews.

Annual Review of Medicine, Volume 10, 1959, edited by David A. Rytand. Annual Reviews, Inc., Palo Alto, Calif., 1959, pp. 448, $7.00.

Textbook of Surgery, seventh edition, edited by Warren H. Cole. Appleton-Century-Crofts, Inc., New York, 1959, pp. 1,248, $17.00.

Mitral Valvulotomy, by Harold J. Stewart and Frank Glenn. Charles C Thomas, Springfield, Ill., 1959, pp. 244, $10.50.

Recent Advances in Cardiology, by Terence East and Curtis Bain. Little, Brown & Co., Boston, 1959, pp. 421, $10.00.

Diseases of Medical Progress, by Robert H. Moser. Charles C Thomas, Springfield, Ill., 1959, pp. 131, $4.75.

The Surgeon and the Child, by Willis J. Potts. W. B. Saunders Co., Philadelphia, 1959, pp. 255, $7.50.

Compendio di Elettrocardiografia, by Vincenzo Masini. Il Pensiero Scientifico, Rome, 1959, pp. 474, 4,500 Lira.

Semeiologia Fonocardiografica, by Giovanni Gigli and Giulio Muiesan. Il Pensiero Scientifico, Rome, 1959, pp. 365, 6,000 Lira.

The Arterial Wall, edited by Albert I. Lansing. Williams & Wilkins Co., Baltimore, 1959, pp. 259, $7.50.

Biochemistry of Blood in Health and Disease, by I. Newton Kugelmass. Charles C Thomas, Springfield, Ill., 1959, pp. 543, $15.75.

The Mediastinum, by Ted F. Leigh and H. Stephen Weens. Charles C Thomas, Springfield, Ill., 1959, pp. 246, $11.50.

Clinical Auscultation of the Heart, by Samuel A. Levine and W. Proctor Harvey. W. B. Saunders Co., Philadelphia, 1959, pp. 657.

The Year Book of Medicine (1959–1960 Year Book Series), edited by Paul B. Beeson et al. The Year Book Publishers, Chicago, 1959, pp. 733, $8.00.

Acute Cardiac Pulmonary Edema, by Sigmund Wasserman. Charles C Thomas, Springfield, Ill., 1959, pp. 123, $4.25.

Angiologie: Pathologie, Klinik und Therapie der Peripheren Durchblutungsstörungen, by Max Ratschow. Georg Thieme Verlag, Stuttgart, 1959, pp. 831, DM 174 ($41.45).

Planning Homes for the Aged, edited by Geneva Mathiasen and Edward H. Noakes. F. W. Dodge Corporation, New York, 1959, pp. 119, $12.75.

Work and the Heart, edited by Francis F. Rosenbaum and Elston Belknap. Paul B. Hoeber, Inc., New York, 1959, pp. 537, $12.00.

The Acute Medical Syndromes and Emergencies: Diagnosis and Treatment, by Albert Salisbury Hyman. Landsberger Medical Books, Inc., New York, 1959, pp. 442, $8.75.

Advances in Cardiology. Vol. 2. Selected Lectures from the Third World Congress of Cardiology, Brussels, 1958, edited by R. Hegglin and E. Lüthy. S. Karger AG, Basel, 1959, pp. 337, sFr. 59.

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Studies in Hypertension

INDEX ISSUE

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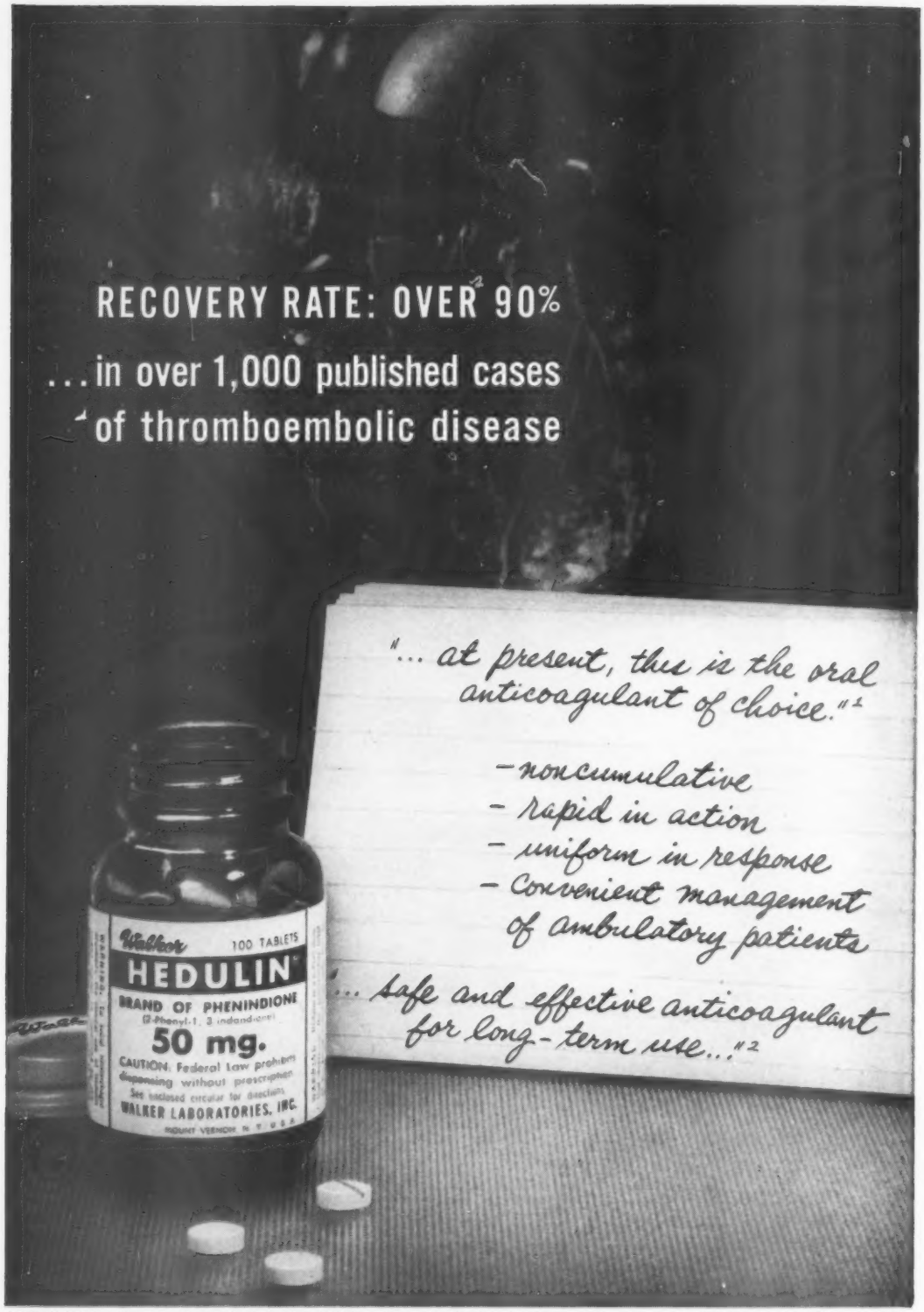
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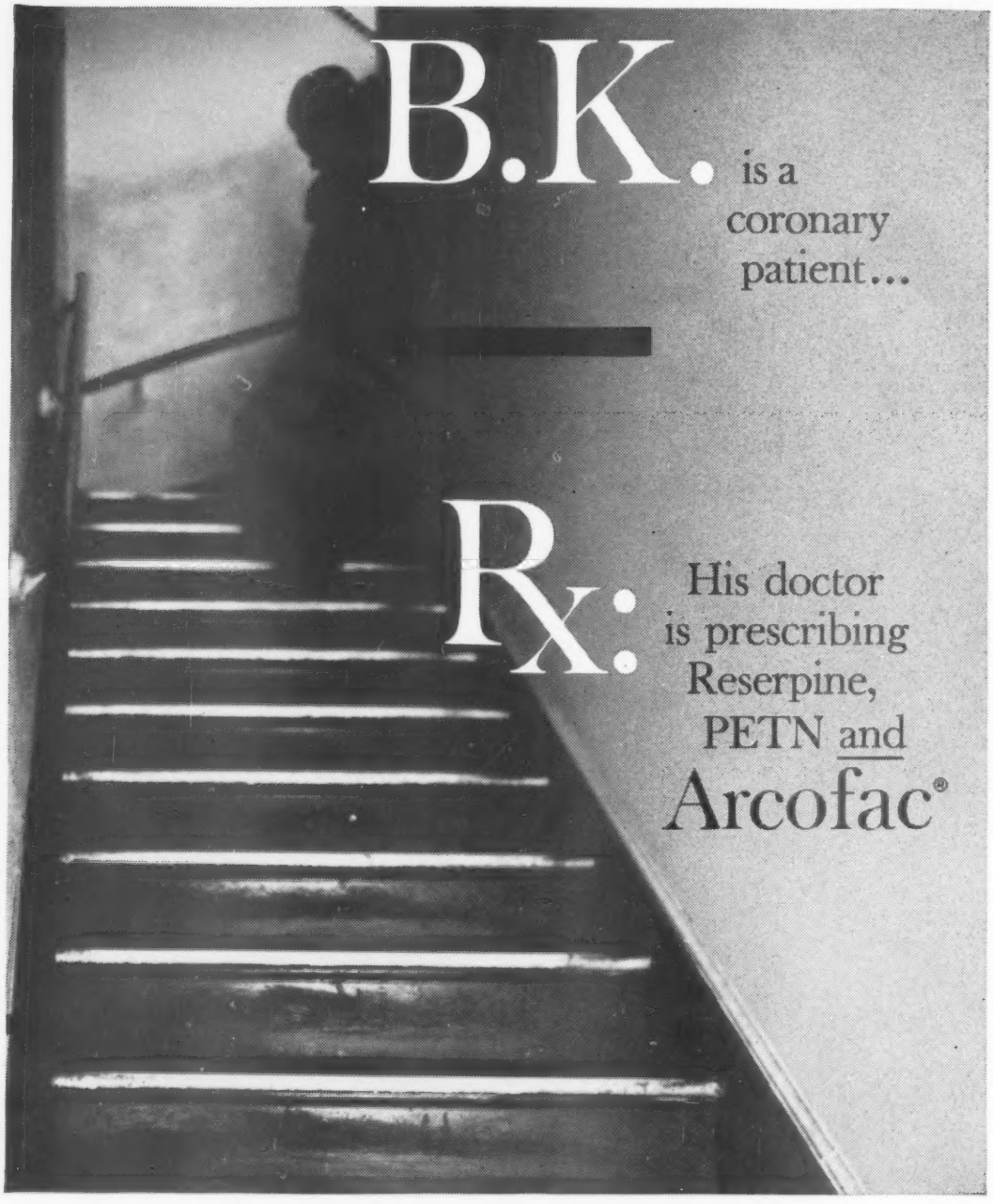

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Why an Encyclopedia of Cardiology? . . . . . A. A. LUISADA 708

Studies in Hypertension

Stress As an Etiologic Factor in Essential Hypertension . . . . LEWIS C. MILLS 711

Convincing, circumstantial evidence is marshalled in the attempt to convict stress as the guilty factor in the etiology of essential hypertension. Outlined are the well known effects of stress on the autonomic nervous system, and the lesser known effects of stress on renal, pituitary and adrenal functions. The data cited clearly indicate that psychic stress can produce transient hypertension and does aggravate existing essential hypertension but further work is necessary to establish whether it is the sole factor.

The Relationship of the Adrenal Cortex to Hypertension
LEWIS C. MILLS AND EFTHIMIOS PONTIDAS 719

Increasing evidence suggests that adrenal cortical hormones may be disturbances of etiologic factors in some types of hypertension. In patients with Cushing's syndrome, congenital adrenal hyperplasia, primary aldosteronism or in those receiving large doses of certain steroids, the hypertension that develops can be cured if proper therapy is started before irreversible cardiovascular changes occur. Some hormonal imbalance is suggested in a second ill-defined group of patients characterized by hypertension, obesity, menstrual disturbances and a tendency to hirsutism, edema, acne and impaired carbohydrate tolerance. Some studies have shown a moderate increase in excretion of aldosterone while other studies have shown normal excretion of steroids in these subjects. It is suggested that an imbalance between groups of adrenal steroid hormones rather than hypersecretion of a single given steroid is responsible for the hypertension in some patients with essential hypertension.

Epidemiology of Hypertension with Particular Reference to the Bahamas. I. Preliminary Report of Blood Pressures and Review of Possible Etiologic Factors
MARVIN MOSER, RICHARD MORGAN, MALCOLM HALE, SIBLEY W. HOOBLER, RICHARD REMINGTON, H. J. DODGE AND ALICE I. MACAULAY 727

A two-year epidemiologic study of the blood pressure of 3,594 Negro subjects in the Bahamas confirms previous observations that the prevalence of hypertension in this area is high. The percentage of males with a blood pressure of 150/90 mm. Hg or more was 25 per cent; of females 30 per cent. Comparison of these data with the blood pressure of white subjects in the United States revealed significantly higher systolic and diastolic blood pressures in both sexes and in all age groups in the Bahamas. It is suggested that the blood pressure of Negroes is higher regardless of areas studied or the level of civilization.

Observations on Flumethiazide in the Treatment of Essential Hypertension
JOSEPH B. ROSENFELD, JOHN BEEM, ALBERT BREST AND JOHN H. MOYER 734

Flumethiazide, 500 mg. given twice daily for two months, was an effective antihypertensive agent in 41 per cent of patients with mild hypertension as measured by blood pressures recorded in the supine position. When rauwolfia and flumethiazide were given in combination, results were better. Curiously enough, the results were better when flumethiazide, rather than rauwolfia, was given prior to the combined therapy. An orthostatic hypotensive effect was noticed when flumethiazide was given alone or in combination.

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A Comparison of Hydrochlorothiazide and Chlorothiazide in the Treatment of Hypertension . . . . . LAWRENCE E. MELTZER, LAMBERT G. EICHNER, ERDAL URAL AND J. RODERICK KITCHELL 741

To remedy human failings in following a salt-restricted diet for the treatment of hypertension, the current fashion in the best medical circles is the use of potent oral diuretic agents in conjunction with antihypertensive agents. These reduce blood pressure secondary to salt loss, either from the extracellular fluid, salt-laden arterial walls, muscles or elsewhere. Comparing hydrochlorothiazide and chlorothiazide in the treatment of seventy-two patients with hypertension, the investigators found that twenty-seven of sixty patients showed greater reduction in blood pressure of 10 per cent or more of the former levels when hydrochlorothiazide was substituted for chlorothiazide. The greater effectiveness of hydrochlorothiazide is believed related to greater ability to increase the excretion of salt in the urine.

Clinical Evaluation of Trimethidinium Methosulfate. A New Ganglioplegic Agent JAMES G. JANNEY, JR., CARLO CACIOLO, GEORGE W. DUANE, S. R. VENUGOPALA REDDY AND A. K. SIMONIDIS 745

Trimethidinium methosulfate, a new vasodilator agent with central and ganglionic blocking effects, controlled elevated blood pressure in twenty patients as well as or better than pentapyrrolidinium. It showed a better and more consistent hypotensive effect, greater and more rapid reduction in severity index and although side effects were more frequent they were less severe and more easily controlled. Addition of hydralazine resulted in a more favorable response with a smaller dose of trimethidinium methosulfate. A significant response was obtained in 85 per cent of the cases, 55 per cent becoming normotensive. The reduction in the average blood pressure levels was 57 mm. Hg systolic and 27 mm. Hg diastolic.

Reviews

Transmembrane Cationic Gradient and Blood Pressure Regulation. Interaction of Corticoids, Catecholamines and Electrolytes on Vascular Cells. WILHELM RAAB 752

The degree of vasoconstrictor effectiveness of intrinsic vascular catecholamines "is determined by the intra-extracellular electrolyte concentration difference, which, in turn, is influenced by the adrenal mineralocorticoids by virtue of their specific ability to deposit sodium intracellularly." This sentence sums up a lifetime study by an outstanding authority of the neurohormonal regulation of blood pressure. In this review the author demonstrates and sketches the complex interaction of corticoids, catecholamines and electrolytes on vascular cells. Therapeutic measures to be effective must (1) decrease catecholamine action on the vascular walls and (2) decrease or deplete the sodium of the body or, more specifically, of the contractile vascular cells.

Experiences with Coarctation of the Aorta CHARLES P. BAILEY, WILLIAM M. LEMMON AND BENJAMIN G. MUSSER 775

A new system of classification for coarctation of the aorta is presented along with the results in fifty-eight patients operated upon over a period of eight years and ten months. There was only one operative (hospital) death in the series (mortality rate 1.7 per cent). The rate of cure by operation for hypertension due to coarctation of the aorta is probably higher than for hypertension caused by any other condition. In 88 per cent the blood pressure in the arms after operation was much lower and remained so. All patients followed up have excellent pulsations and/or normal blood pressures in the lower extremities. The surgical technics are outlined. Since children and young adults withstand surgery better than the mature adult, surgery is best performed on the patient who is between six and eighteen years of age.

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*Biegeleisen, H.I.; Clinical Medicine; Oct., 1955
*Roberts, J.T., Clinical Medicine; Nov., 1957
**Batterman, R.C., et al., Scientific Exhibit, A.M.A. Clinical Meeting, Dec., 1958

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Report on Therapy

Diuretic Therapy in Syndromes Associated with Sodium and Water Retention
JOHN H. MOYER AND MORTON FUCHS 786

This paper reviews the pharmacodynamics and clinical use of mercurial and non-mercurial diuretic agents in syndromes associated with sodium and water retention. Chlorothiazide, flumethiazide and hydrochlorothiazide are effective diuretic drugs. The natriuretic effect is the same for all three but hydrochlorothiazide shows a greater chlorouretic than natriuretic effect and excretion of potassium is greater. With this drug a hypochloremic hypopotassemic alkalosis occurs more readily. The authors urge maximum therapy in the treatment of heart failure. They maintain that the number of patients in whom severe and progressive heart failure develops from inadequate therapy is greater than the number who suffer side effects associated with overtreatment. Various treatment schedules are suggested and the use of diuretics in premenstrual edema, edema of pregnancy, renal disease, hepatic disease and iatrogenic edema is outlined.

New Methods

Left Ventricular Angiocardiography in the Diagnosis of Persistent Atrioventricular Canal and Related Anomalies
EUGENE BRAUNWALD, ANDREW G. MORROW AND THEODORE COOPER 802

Left ventricular selective angiocardiography and indicator-dilution curves permit precise preoperative diagnosis in patients with persistent atrioventricular canal and related complex defects. These studies are indicated when clinical or catheterization findings are considered atypical. Selected clinical examples of the value of the technics are provided. In patients suspected of having an atrial septal defect, the presence of any clinical findings suggestive of mitral valve involvement, pulmonary hypertension or left ventricular hypertrophy points to a complex lesion requiring selective angiocardiography.

Historical Milestones

Functional Heart Disease in the Civil War (Da Costa, 1871) . . . SAUL JARCHO 809

"War is hell," many an officer and enlisted man has growled. Yet, to give the devil his due, medical science has often advanced in leaps and bounds during and immediately after wars. The classic work by Da Costa on functional heart disease in the Civil War is such an example. This month's historical milestone describes Da Costa's clinical observations in 1871 on the clinical picture of the irritable heart which the sophisticated cardiologist of the twentieth century finds hard to improve upon.

Diagnostic Shelf

Synchronization and Accrochage in the Presence of Incomplete Heart Block
JOSEPH H. YAHINI 818

The phenomenon of synchronization and accrochage consists of synchronous contractions of the atria and ventricles in spite of the presence of complete heart block. This report describes an electrocardiogram presenting first and second degree A-V block, concealed conduction and skipped P waves which suggest auriculoventricular synchronization.

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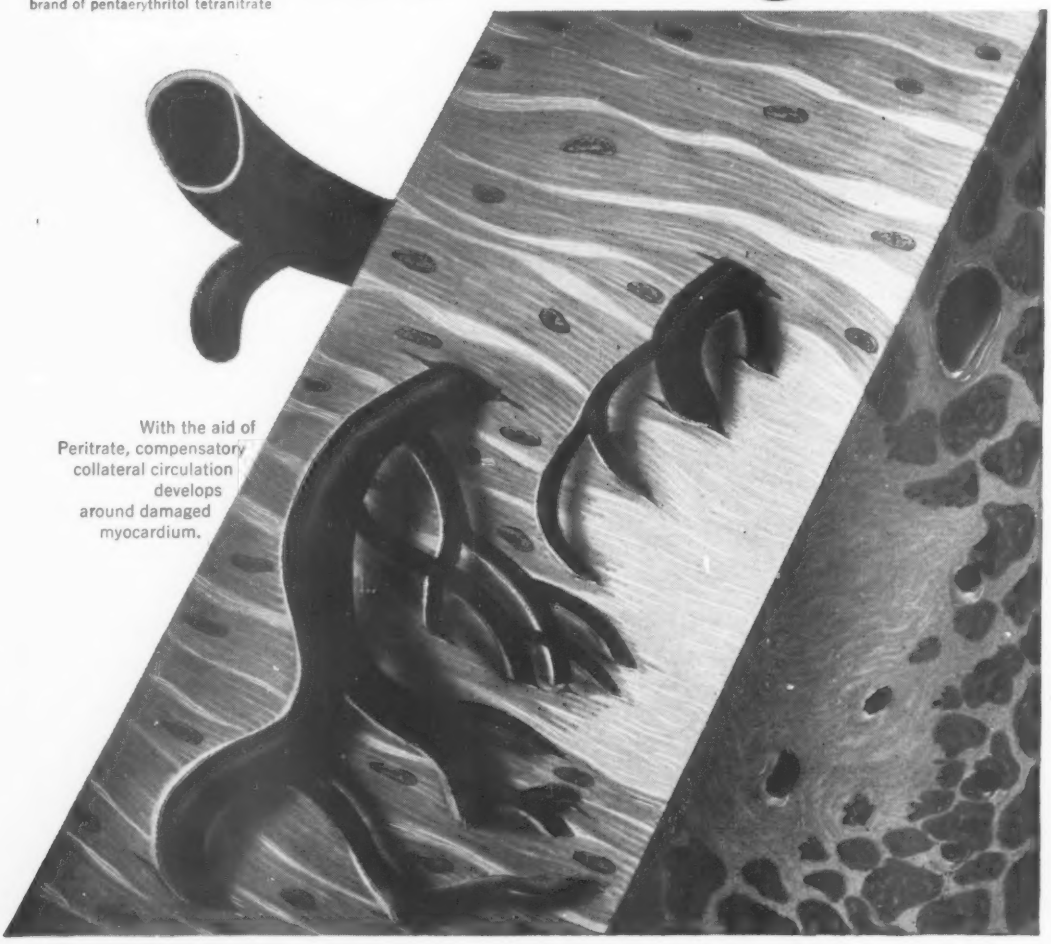

With the aid of Peritrate, compensatory collateral circulation develops around damaged myocardium.

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Case Reports

The Murmur of Mitral Stenosis: Modification by A-V Dissociation
MARVIN A. SACKNER, DORIS SOMERSON AND SAMUEL BELLET 821

Describing some interesting modifications of the auscultatory phenomenon resulting from A-V dissociation in a patient with mitral stenosis, these studies confirm that atrial ejection of blood into the ventricle prior to ventricular systole is responsible for the presystolic rumble. The Valsalva maneuver was of value in separating the opening snap from a physiologic split second sound. During this maneuver the opening snap is delayed and the 2-OS distance remains the same or is increased.

Escape-Capture Bigeminy. Bigeminal Rhythm Due to 3:1 S-A Block Associated with A-V Dissociation . . . . . L. M. SANGHVI AND K. BANERJEE 825

Pseudoreciprocal or escape-capture bigeminy resulting from S-A block is rare. There are only three instances recorded in the literature and in one other case the possibility of such a rhythm has been suggested. In each the bigeminal rhythm was associated with 2:1 S-A block. This article describes a patient with escape-capture bigeminy due to 3:1 S-A block associated with A-V dissociation. The transient episodes of S-A block were apparently responsible for the spells of dizziness which the patient experienced.

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The Program Committee asks your cooperation and help in stimulating any worker in the field of cardiovascular disease to submit abstracts of scientific work for selection for presentation at the Annual Meeting of the American College of Cardiology to be held in Indianapolis at the Claypool Hotel from May 23 to May 28, 1960. Such abstracts must be submitted on or before February 15, 1960 to: JOHN S. LADUE, M.D., Chairman, Program Committee, 115 East 61st Street, New York 21, New York.

Index to Advertisers on page 52

DISSOLVES INTRAVASCULA C

NOT JUST A NEW DRUG... *A NEW THERAPY*

TRADEMARK

Fibrinolysin (Human)

1. Moser, K.M.: J.A.M.A. *167*:1695 (Aug. 2) 1958.
2. Clifton, E.E.: J. Am. Geriatrics Soc. *6*:118, 1958.
3. Sussman, B.J., and Fitch, T.S.P.: J.A.M.A. *167*:1705 (Aug. 2) 1958.
4. Singher, H.O., and Chapple, R.V.: Clin. Med. *6*:439 (March) 1959.

ORTHO PHARMACEUTICAL CORPORATION, RARITAN, N. J.

in thrombophlebitis and pulmonary embolism

Clinically proved,[1-3] ACTASE has a specific lytic effect upon the venous thrombus or pulmonary embolus. Patients respond rapidly, often dramatically, to the clot-dissolving action of an intravenous infusion of this physiologic fibrinolysin.[4] A significant decrease in length of hospitalization following thrombophlebitis, as well as a reduction in the threat of pulmonary embolism, is now possible. In one series of patients with deep thrombophlebitis, some of whom had previously suffered pulmonary emboli, no occurrence of pulmonary emboli was reported following administration of ACTASE.[1]

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- *reduces frequency and severity of attacks*
- *reduces the need for nitroglycerin*

Supplied—Boxes of 60 and 120

1. Feinblatt, T. M., and Ferguson, E. A.: New Eng. J. Med. 256:331 (Feb.) 1957.
2. Kupersmith, I. H.: International Record of Medicine, Vol. 171 No. 10 (Oct.) 1958.
3. Berry, J. W., and Roach, T. C.: Circulation, Vol. 17, No. 6 (June) 1958.

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When more than 900 calories are permitted, the daily allotment (½ pound) of Metrecal may be increased—or it may be used with low-calorie foods.

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(1) Antos, R. J., to be published. (2) Tullis, I. F., to be published.

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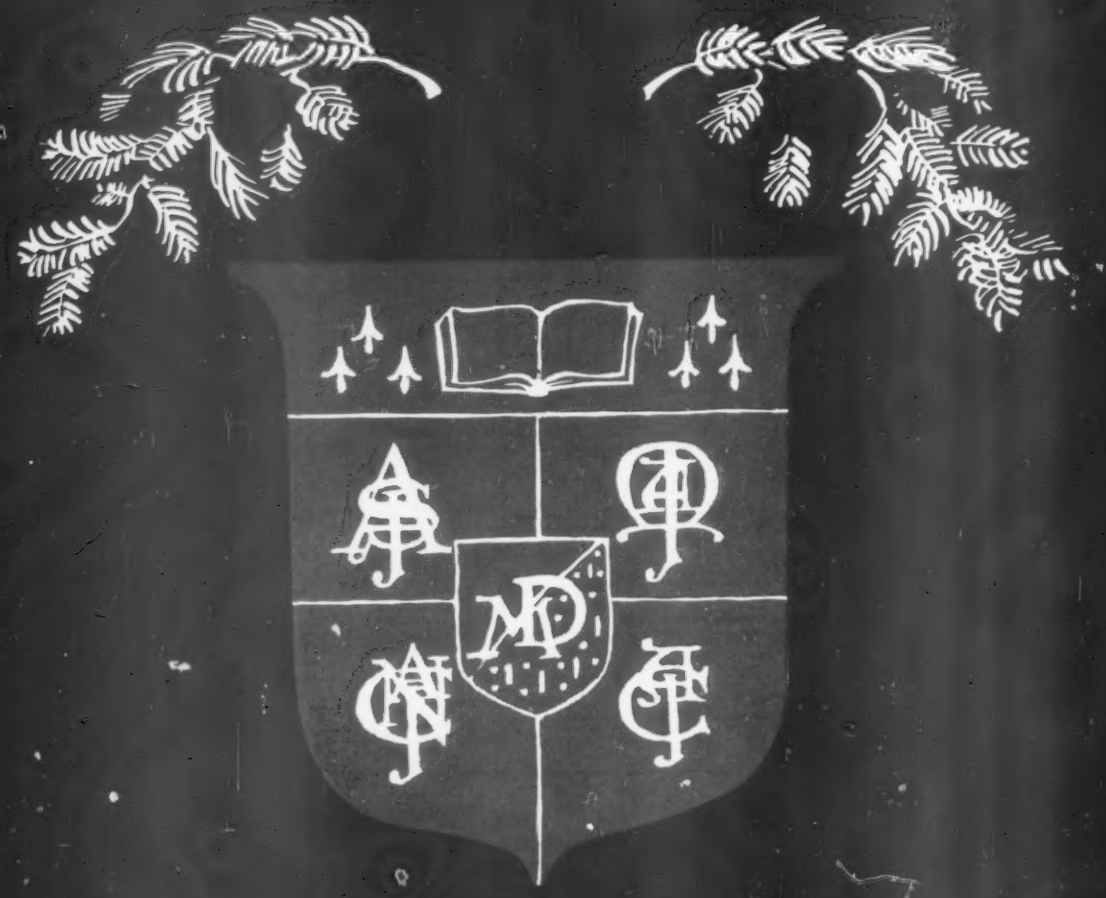

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of
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for
angina pectoris

1 **rapid onset**

2 **prolonged action**

3 **consistent effect**

4 **unusual safety**

ISORDIL significantly reduces the number, duration, and severity of anginal attacks, often when other long-acting coronary vasodilators fail. Exercise tolerance is increased, pain decreased, and the requirements for nitroglycerin either drastically curtailed or eliminated.

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Sherber,[2] summarizing his experience with ISORDIL, states it is "the most effective medication for the treatment of coronary insufficiency available today."

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Markedly reduces number of anginal attacks:

Albert[5] found that of 29 patients receiving ISORDIL, 25 responded well, 1 moderately well, and 1 not at all. Effectiveness could not be judged in 2 patients. For those who responded well, the frequency of anginal attacks was quickly reduced from a daily average of 5 to 1.2. Continued use of ISORDIL further reduced the frequency of attacks.

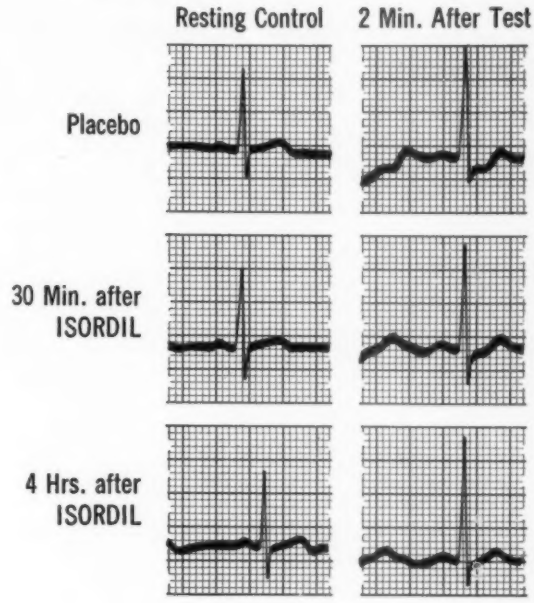
Increases tolerance to exercise and stress:

Electrocardiographic response following the Master two-step test has clearly established a more favorable balance between oxygen supply and demand to the myocardium with ISORDIL therapy. Eight of 10 patients administered ISORDIL in studies by Russek[6] showed considerably less abnormality in the post-exercise electrocardiogram than before treatment.

Rapid onset and prolonged action a function of solubility and metabolism:

Pharmacologic studies indicate that the rapid onset and prolonged action shown by ISORDIL are related to its high solubility and low rate of metabolism.[7] Incubation with liver slices suggest rapid absorption and delayed inactivation by the liver.

Master Test Responses (Lead V_4) in a 58-Year-Old Male with Angina Pectoris[6]



unprecedented effectiveness in angina pectoris

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- **Reduces number, duration, and severity of anginal attacks**

"Isordil is a new and effective agent for therapy of angina pectoris."—Russek[6]

Composition: Each white, scored tablet of ISORDIL (Isosorbide Dinitrate) contains 10 mg. of 1,4,3,6-dianhydro-sorbitol-2,5-dinitrate.

Action: Following oral administration of ISORDIL, the effects of coronary vasodilatation are apparent within 15 to 30 minutes and persist for 4 to 5 hours.

Indications: ISORDIL is indicated for the therapeutic and prophylactic management of angina pectoris and coronary insufficiency. It is often useful in patients only partially responsive to other long-acting coronary vasodilators.

Dosage: ISORDIL is administered orally. Average dose is one tablet (10 mg.) taken one half hour before meals and at bedtime. Individualization of dosage may be necessary for optimum therapeutic effect; dosage may vary from 5 mg. to 20 mg. q.i.d.

Side Effects: Side effects are few, infrequent, and mild. Transitory headache, common to effective nitrate or nitrite therapy, has occurred. This usually responds to administration of acetylsalicylic acid, and disappears with continued therapy. When headache is persistent, reduction in dosage may be required.

Caution: ISORDIL should be given with caution in patients with glaucoma.

Supplied: Bottles of 100.

References: 1. Riseman, J.E.F., et al.: Circulation **17:**22-39 (Jan.) 1958. 2. Sherber, D.A.: Personal Communication (Oct., 1959). 3. Case Reports on File, Ives-Cameron Company (1958-1959). 4. Summary of Case Reports on File, Ives-Cameron Company (1958-1959). 5. Albert, A.: Personal Communication (Oct., 1959). 6. Russek, H.I.: Personal Communication (Oct., 1959). 7. Harris, E., et al.: Personal Communication (Oct., 1959).

ISORDIL

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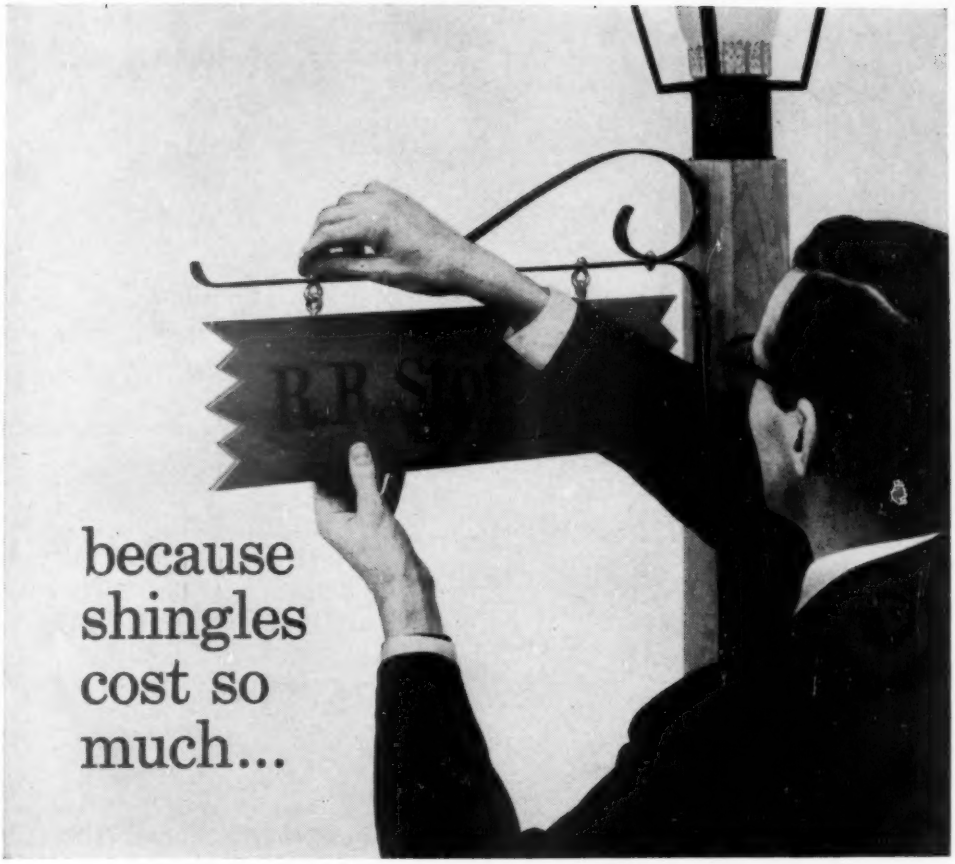

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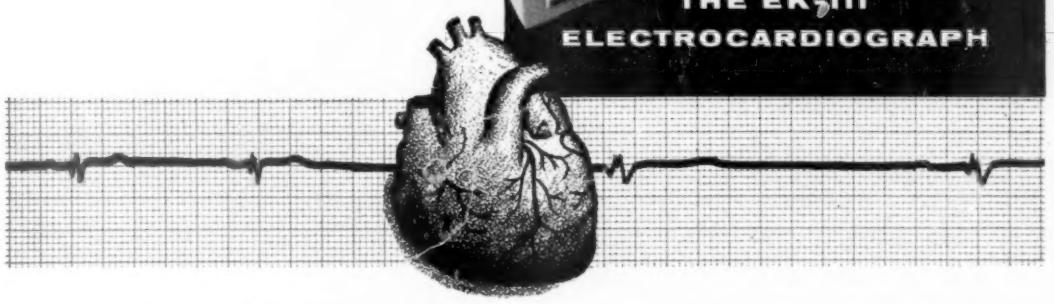

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Circulation, Vol. X, No. 4

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relief comes fast and comfortably

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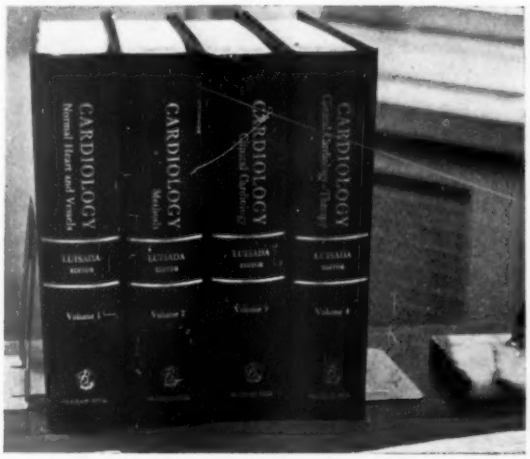

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AJC/59

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Weight 176 lbs.

27 pounds lost in 19 days; ascites and

RECORD OF TREATMENT (At a leading New York City hospital. Photos used with permission of the patient.)

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pre-eminently effective whenever diuresis is desired

Indicated in: congestive heart failure . . . nephrosis and nephritis . . . toxemia of pregnancy . . . premenstrual edema . . . edema of pregnancy . . . steroid-induced edema . . . edema of obesity

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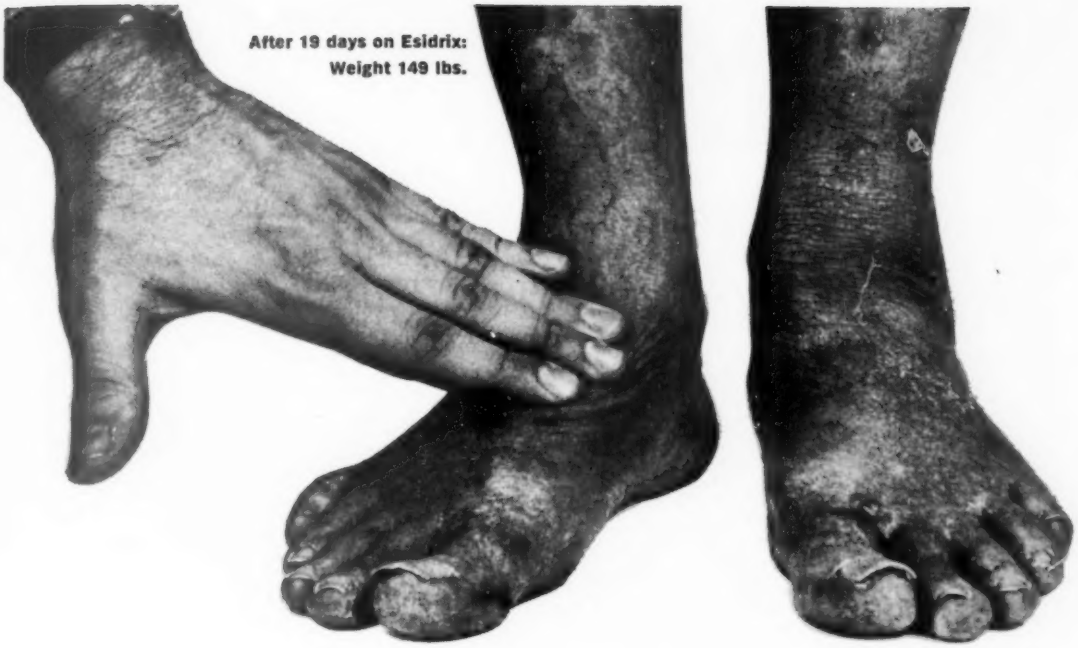
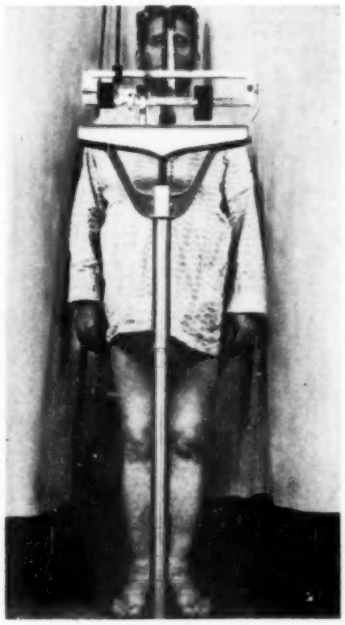


pedal edema reduced with Esidrix

H. K., 44 years old, was admitted to the hospital on 3/3/59 with complaints of *swollen abdomen, swelling of both legs and exertional dyspnea.* These symptoms had been intensifying over a three-week period. The patient's history included heavy drinking since the age of 18, and one prior admission to the hospital in 1954 with ascites and pedal edema. Diagnosis, at that time, was Laennec's cirrhosis, and the patient responded well to a regimen of diuretics, salt restriction and multivitamins. There was no recurrence up to that leading to his current admission.



Clinical findings worthy of note: Eyes — conjunctivae and sclerae slightly icteric. Chest—diaphragm elevated. Abdomen — girth enlarged, definite fluid wave. Liver palpated 4 fingerbreadths below the costal margin; no other palpable viscera. Extremities—pedal edema (4+).

The patient is well developed and not in acute distress. Blood pressure, 140/80 mm. Hg; pulse, 112/min.; respiration, 20/min. Impression: Laennec's cirrhosis—decompensated.

Treatment: Mercurial diuretic on 3/3 and 3/4, followed by Esidrix, 50 mg. b.i.d., from 3/5 to 3/23 when patient signed out of hospital. Esidrix induced copious diuresis resulting in almost complete disappearance of edema.

2/2714MK

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Riseman, J. E. F., *et al.:* Circulation *17*:22, 1958

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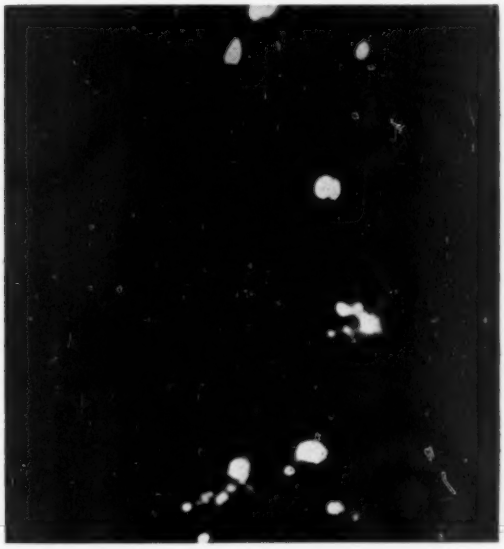
WITHOUT CLARIN, turbid blood serum five hours after a fat meal: This unretouched dark-field photomicrograph (2500X) shows potentially hazardous fat concentrations circulating in the blood stream of a patient after a standard fat meal.



WITH CLARIN, clear blood serum five hours after a fat meal: After eating a standard fat meal as at left, the same patient has taken one sublingual Clarin tablet. Note marked clearing effect and reduction in massive fat concentrations in this unretouched photomicrograph (2500X).

CLARIN is sublingual heparin potassium. One mint-flavored tablet taken after each meal effectively "causes a marked clarification of postprandial lipemic serum."[1] Clarin facilitates the normal physiologic breakdown of fats, with no effects on the blood-clotting mechanism.[1] It therefore provides important benefits for your postcoronary patients.

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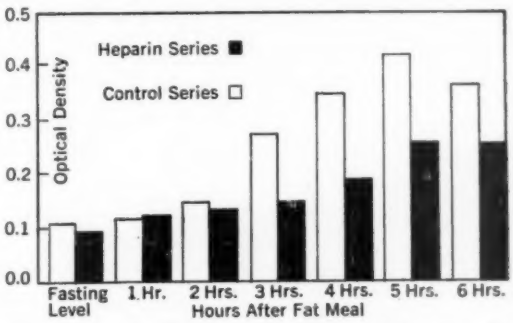
Dosage: After each meal, hold one tablet under the tongue until dissolved.

Supplied: In bottles of 50 pink, sublingual tablets, each containing 1500 I.U. heparin potassium.

1. Fuller, H. L.: Angiology *9*:311 (Oct.) 1958.
2. Shaftel, H. E., and Selman, D.: Angiology *10*:131 (June) 1959.



Average serum optical density in 36 patients after fat meal with and without sublingual heparin.[2]

*Registered trade mark. Patent applied for.

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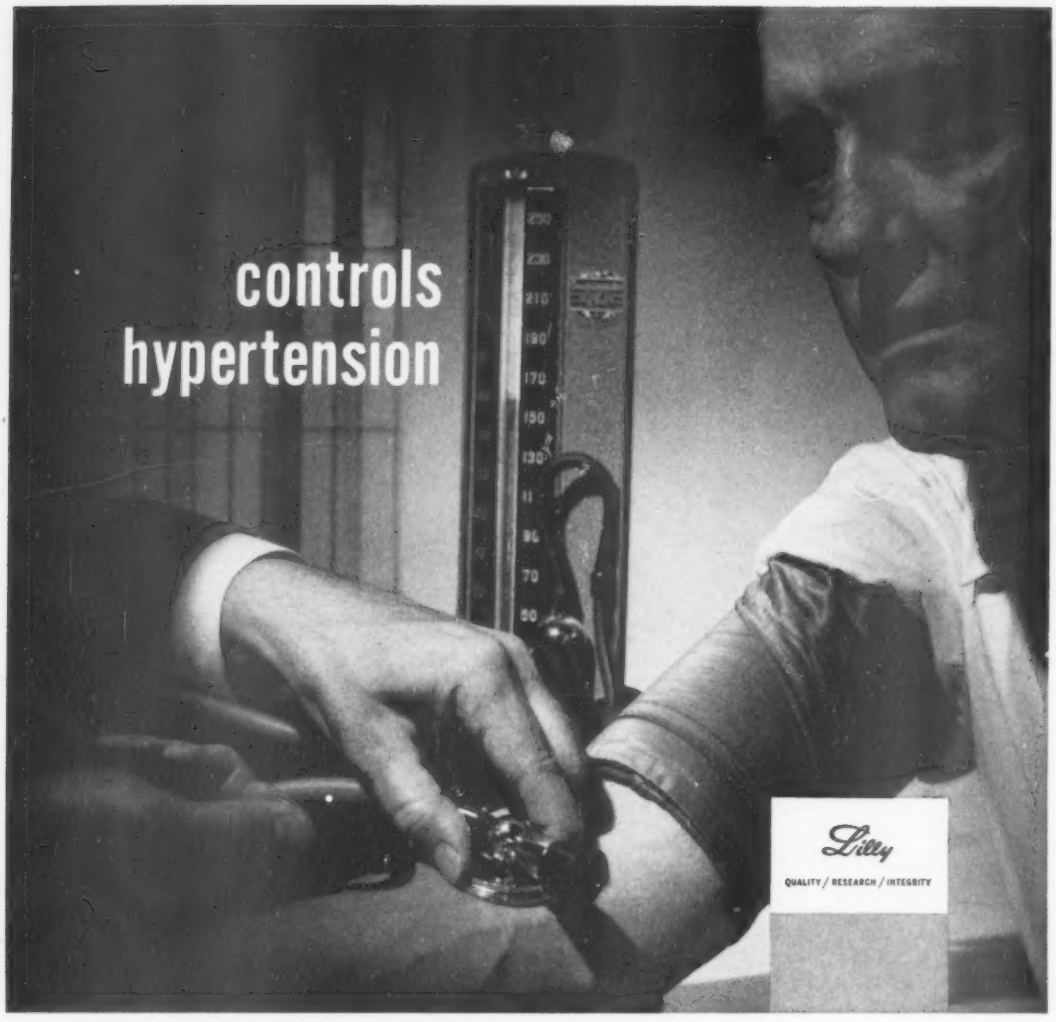

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1. Geriatrics, *12*:185, 1957.
2. J. Indiana M.A., *48*:603, 1955.

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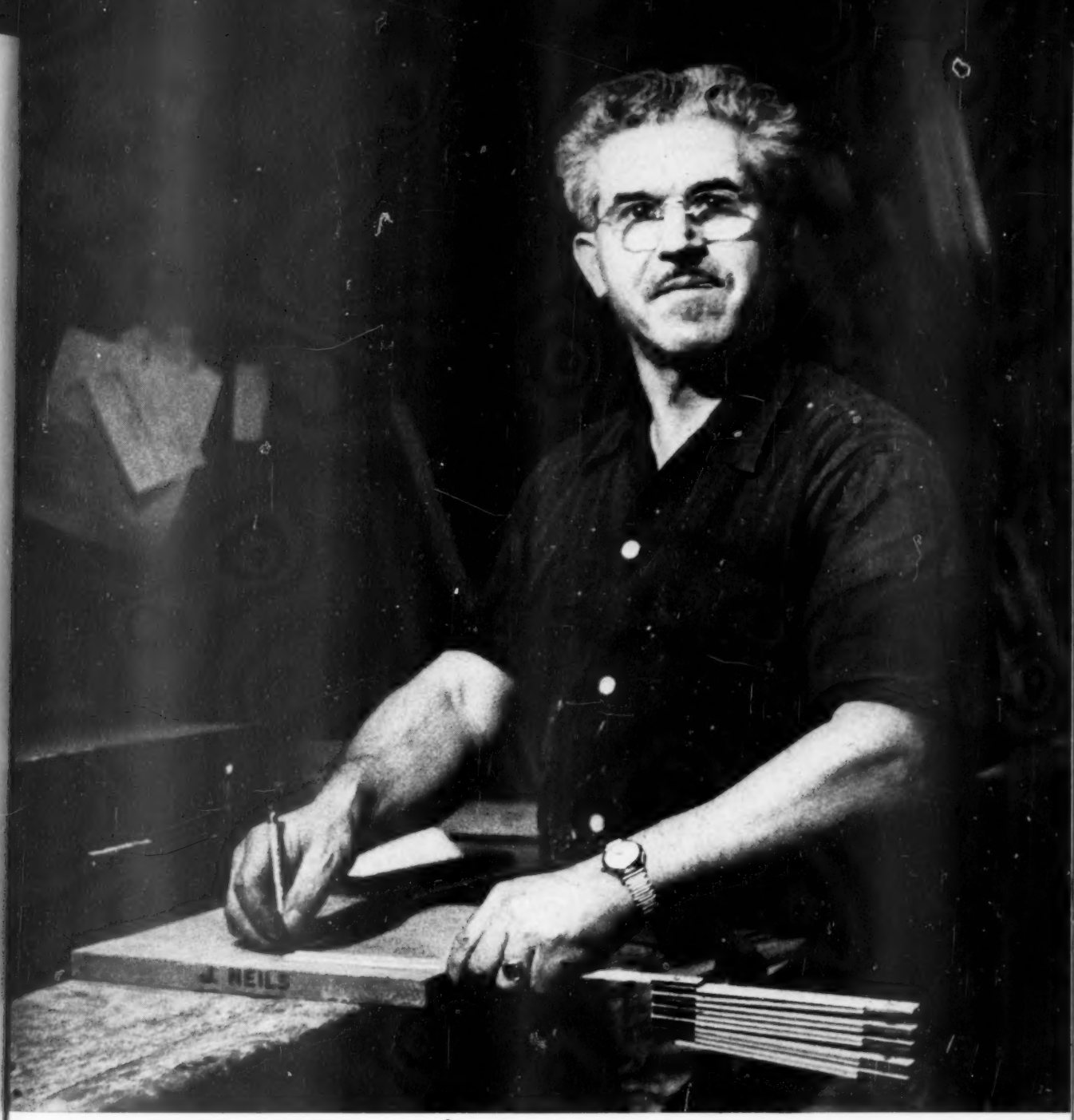

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This normally active angina patient who can do a satisfying day's work without discomfort or the dread of a severe attack is typical of those controlled by METAMINE® SUSTAINED—aminotrate phosphate, 10 mg. (Leeming). A simple protective medication (1 tablet on arising and 1 before the evening meal), METAMINE SUSTAINED eliminates anginal episodes altogether, or greatly reduces their severity and frequency. Many patients refractory to other drugs of this type are aided by METAMINE SUSTAINED.[2]

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Krantz, J. C., Jr.: The restless patient—A psychologic and pharmacologic viewpoint. Current M. Digest 25:68, Feb. 1958.

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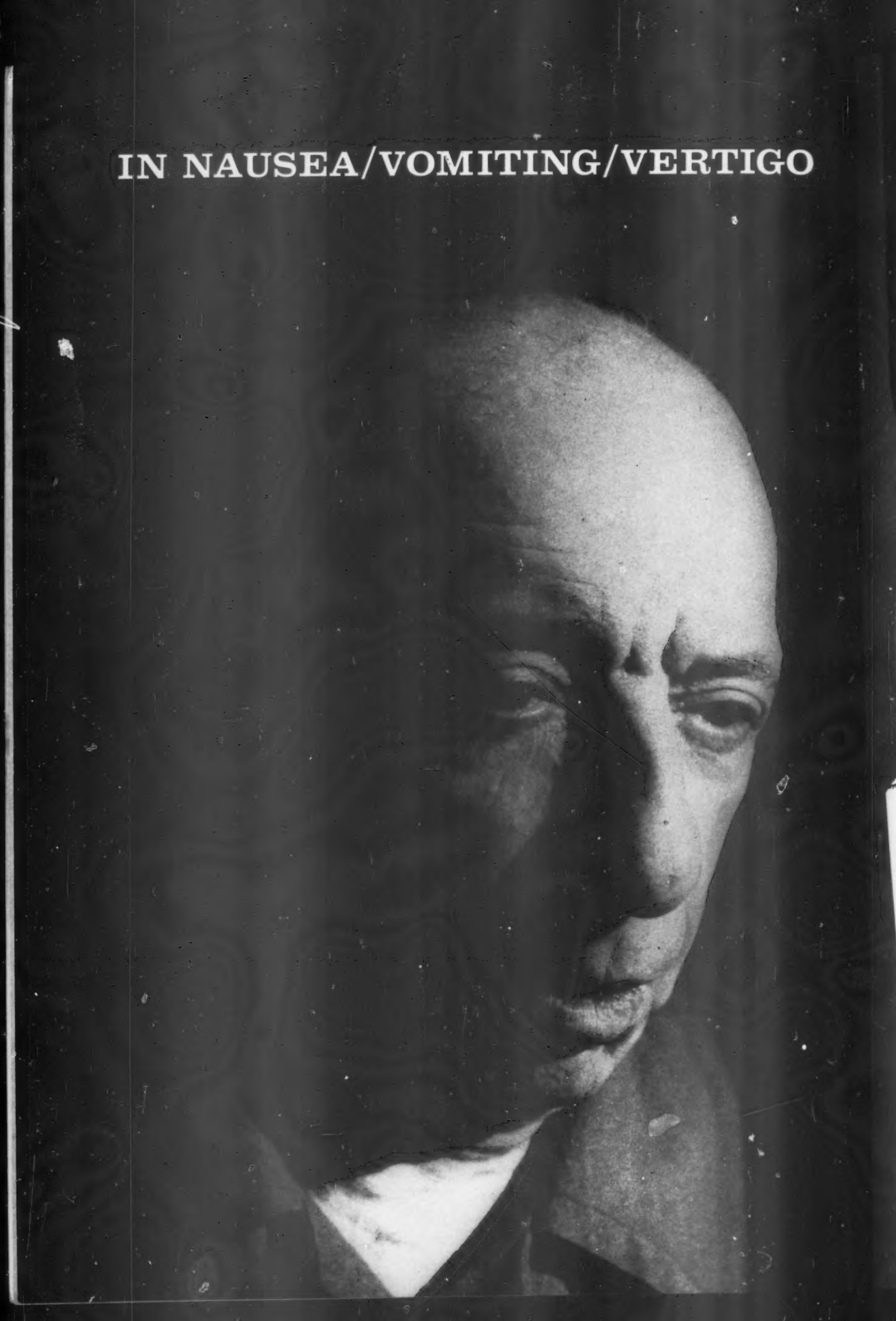

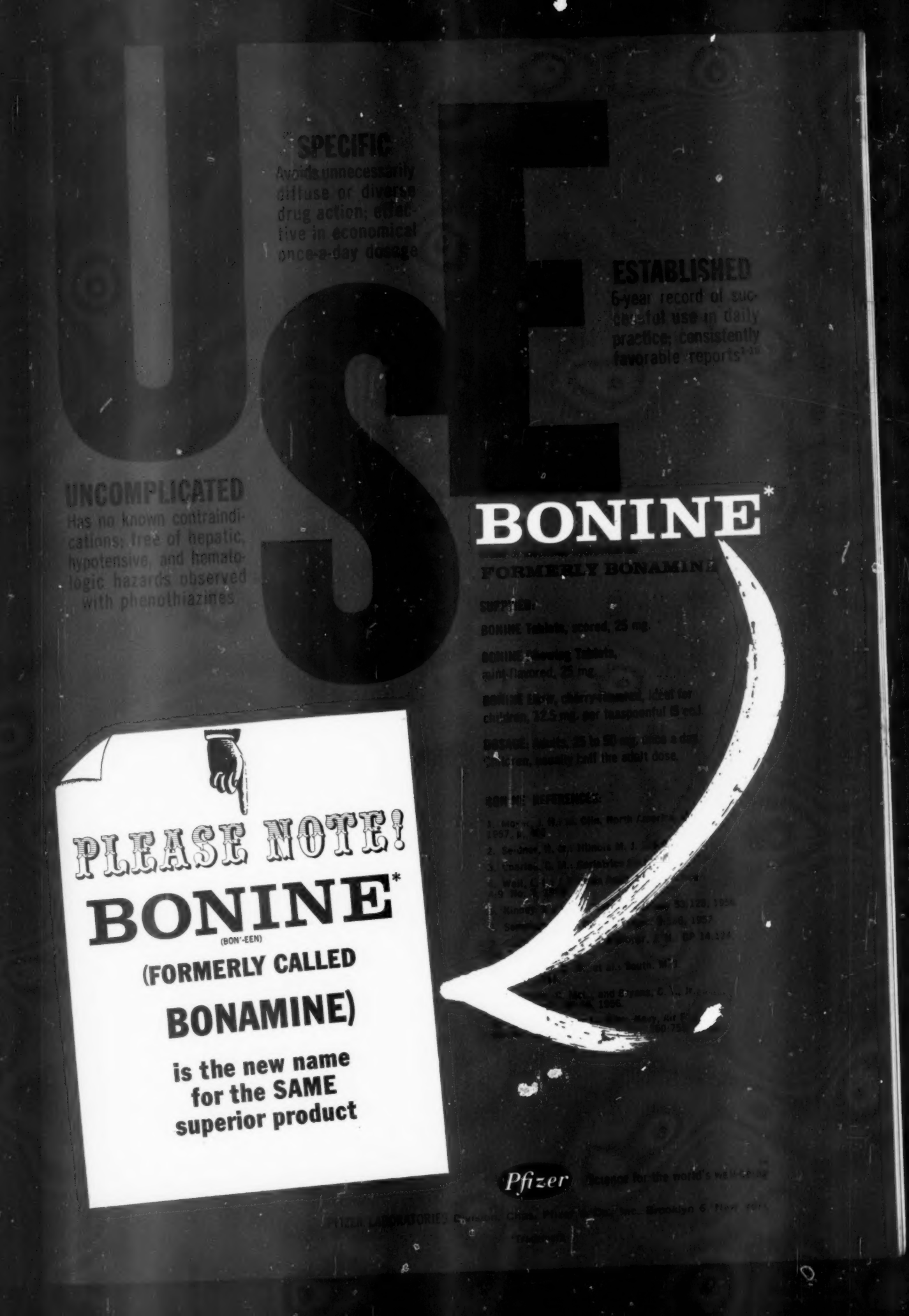
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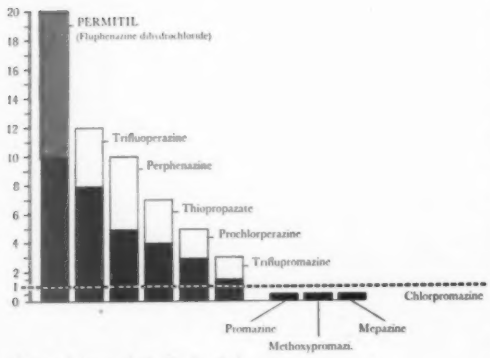

Adapted from Ayd, F. J., Jr.[3]

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References: 1. Freyhan, F. A.: Psychopharmacology Frontiers, Boston, Little, Brown and Co., 1959, p. 7. 2. Ayd, F. J., Jr.: Fluphenazine: its spectrum of therapeutic application and clinical results in psychiatric patients, Current Therapeutic Research, 1:41 (Oct. 15) 1959. 3. Ayd, F. J., Jr.: The current status of major tranquilizers, in press.

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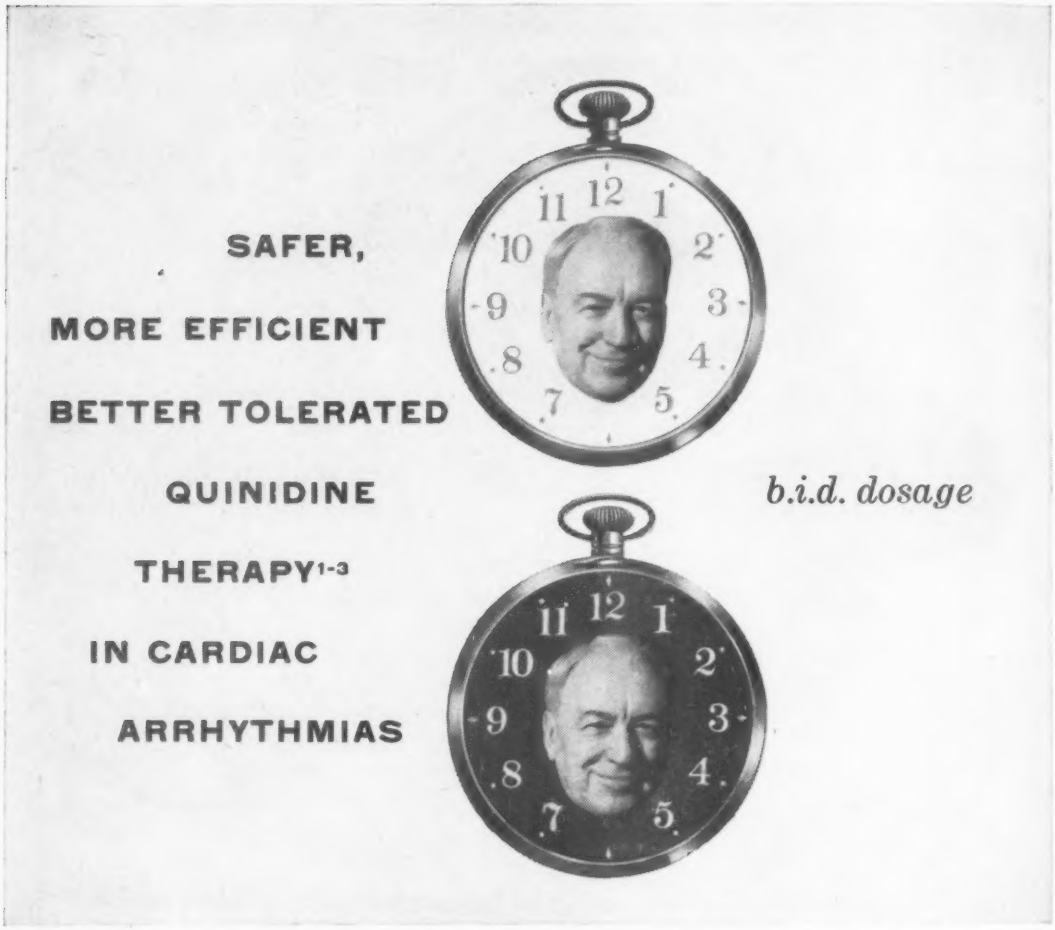

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1. Bellet, S.; Finkelstein, D., and Gilmore H.: A.M.A. Archives Int. Med. 100:750, 1957.
2. Bellet, S.: Amer. Heart J. 56:479, 1958.
3. Finkelstein, D.: Penn. Med. J. 61:1216, 1958.

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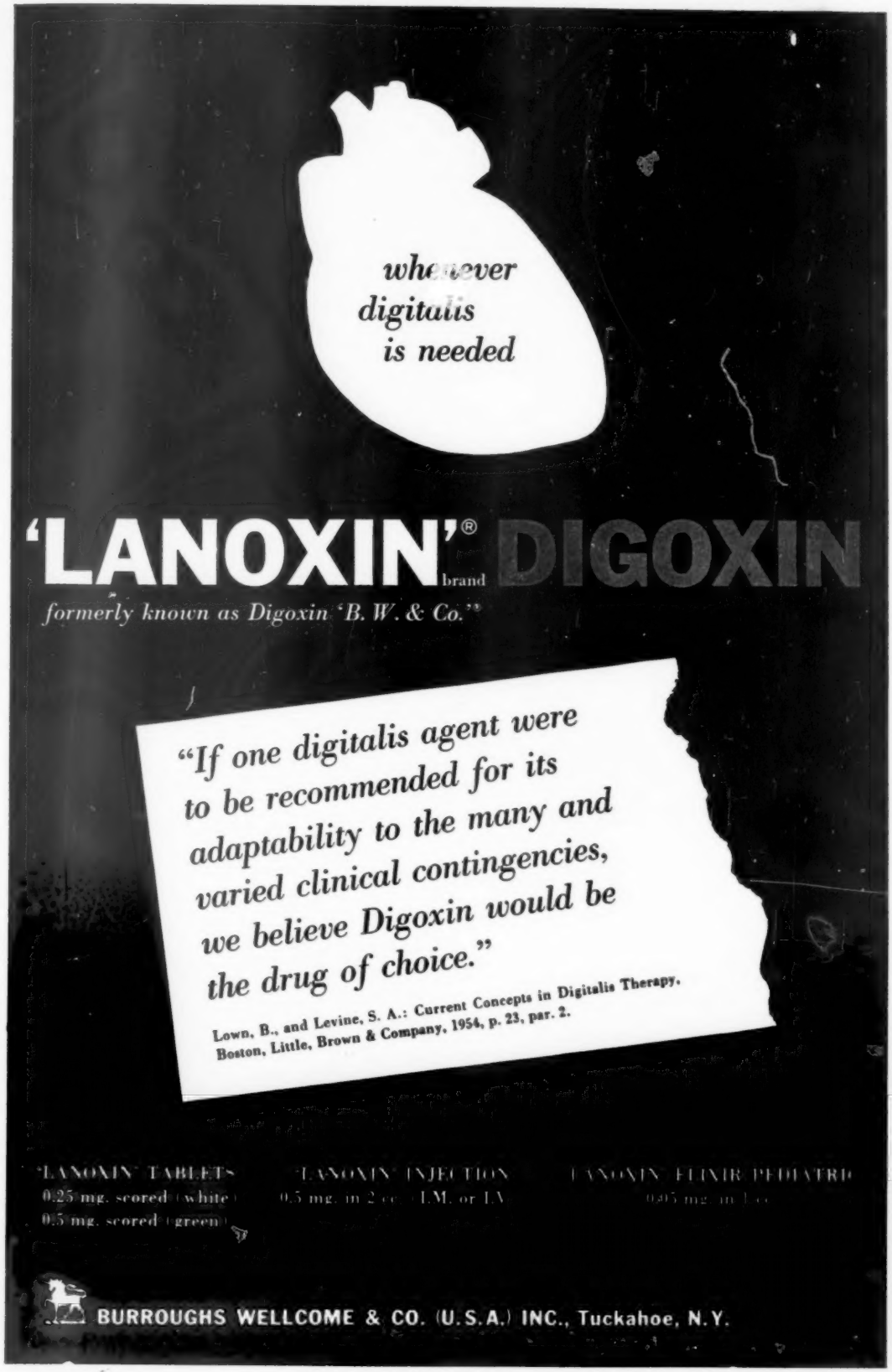
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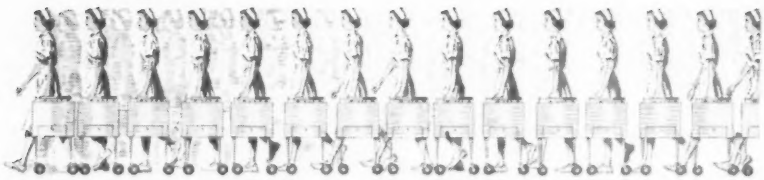

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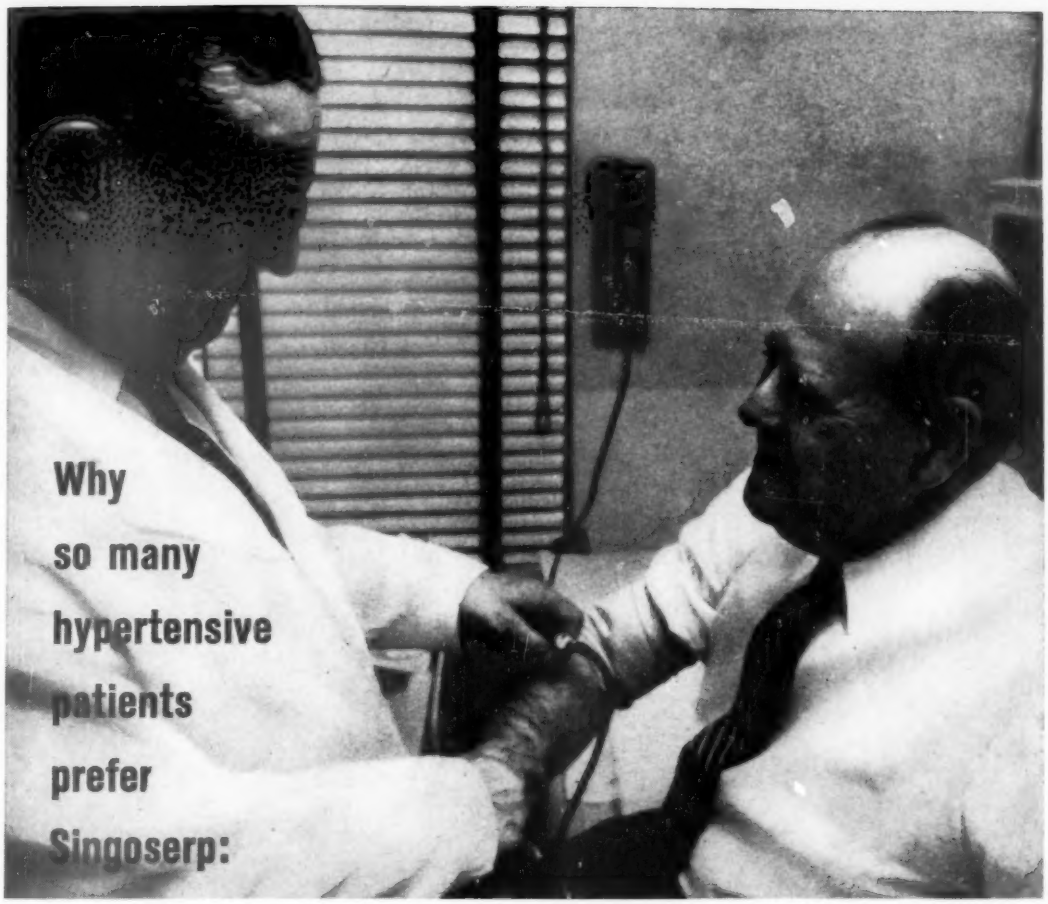

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*Herrmann, G. R., Vogelpohl, E. B., Hejtmancik, M. R., and Wright, J. C.: J.A.M.A. **169**:1609 (April 4) 1959.

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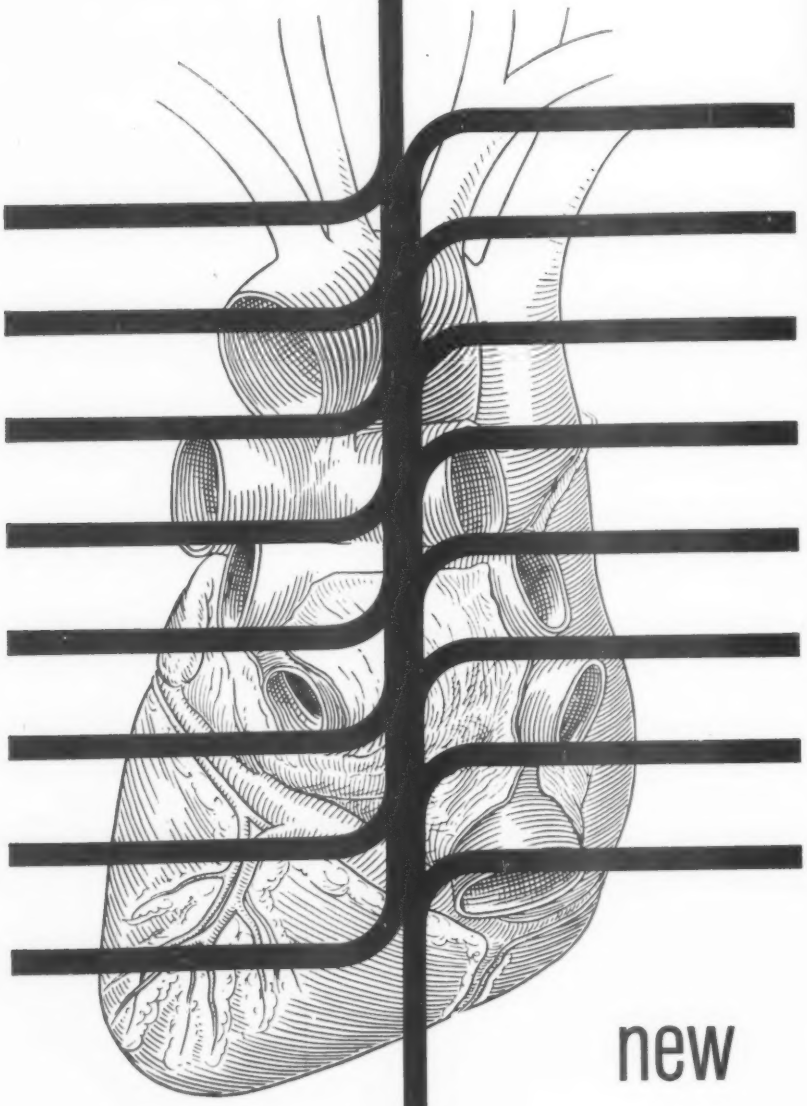

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Patients	*Age*	*Diagnosis*	*Usual Dose*	*Duration of Treatment*
31	40's-70's	Angina pectoris. "About one-half were severely ill."	15-30 mg/day	1-9 mos.

Results: "Over 70 per cent of the patients reported notable benefits. . . ."

Marplan creates a more confident mental climate — The profound antidepressive action of Marplan also controls the components of anxiety and hopelessness, which so often aggravate angina pectoris. Patients display a "more cheerful outlook,"[1] improving the chances of success of the entire prophylactic regimen.

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References: 1. R. W. Oblath, paper read at American Therapeutic Society, 60th Annual Meeting, Atlantic City, N. J., June 6, 1959. 2. G. C. Griffith, *Clin. Med.*, 6:1555, 1959.

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1. Spielman, A.D.: Mich. Acad. Gen. Prac. Symposium, Detroit, 1959.
2. Alfaro, R. D. and Gracanin, V.: *to be published.*

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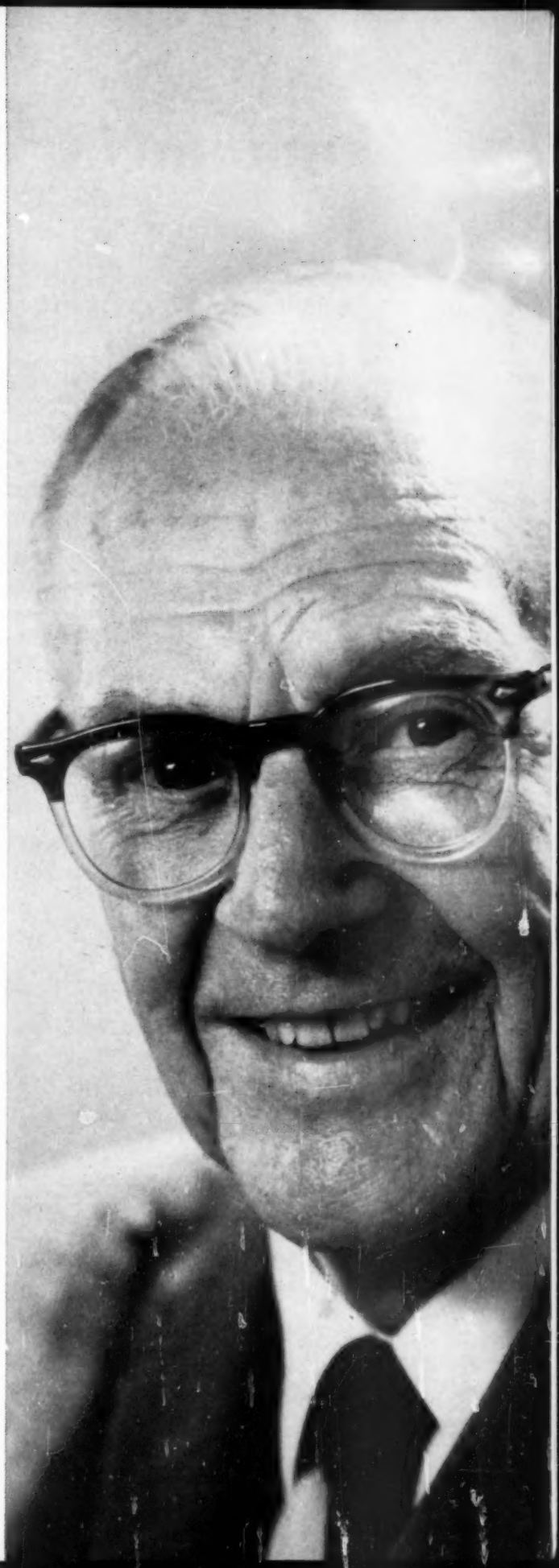

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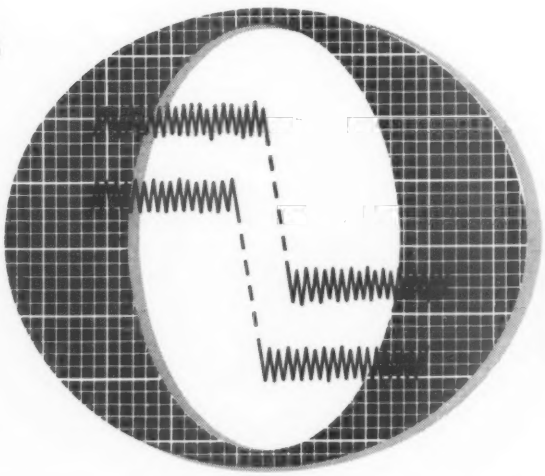

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1. Dunsmore, R.A., et al.: Am. J. M. Sc. *236*:483 (Oct.) 1958. 2. Blaquier, P., et al.: Univ. Michigan M. Bull. *24*:409 (Oct.) 1958. 3. Smirk, F.H.: Submitted for publication. 4. Janney, J.F.: Submitted for publication. 5. Council on Drugs, A.M.A.: J.A.M.A. *166*:640 (Feb. 8) 1958. 6. Freis, E.D., and Wilson, I.M.: Circulation *13*:856 (June) 1956. 7. Moyer, J.H., et al.: A.M.A. Arch. Int. Med. *98*:187 (Aug.) 1956. 8. Moyer, J.H., et al.: Am. Pract. & Dig. Treat. 7:1765 (Nov.) 1956. 9. Dunsmore, R.A. In Tislow, R.F., et al.: Scientific Exhibit. Presented at Annual Convention of A.M.A., San Francisco, June 23-27, 1958.

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References: 1. Russek, H. I.: Postgrad. Med. *19*:562 (June) 1956. 2. Russek, H. I.: Presented at the Symposium on the Management of Cardiovascular Problems of the Aged, Dade County Medical Association, Miami Beach, April 12, 1958.

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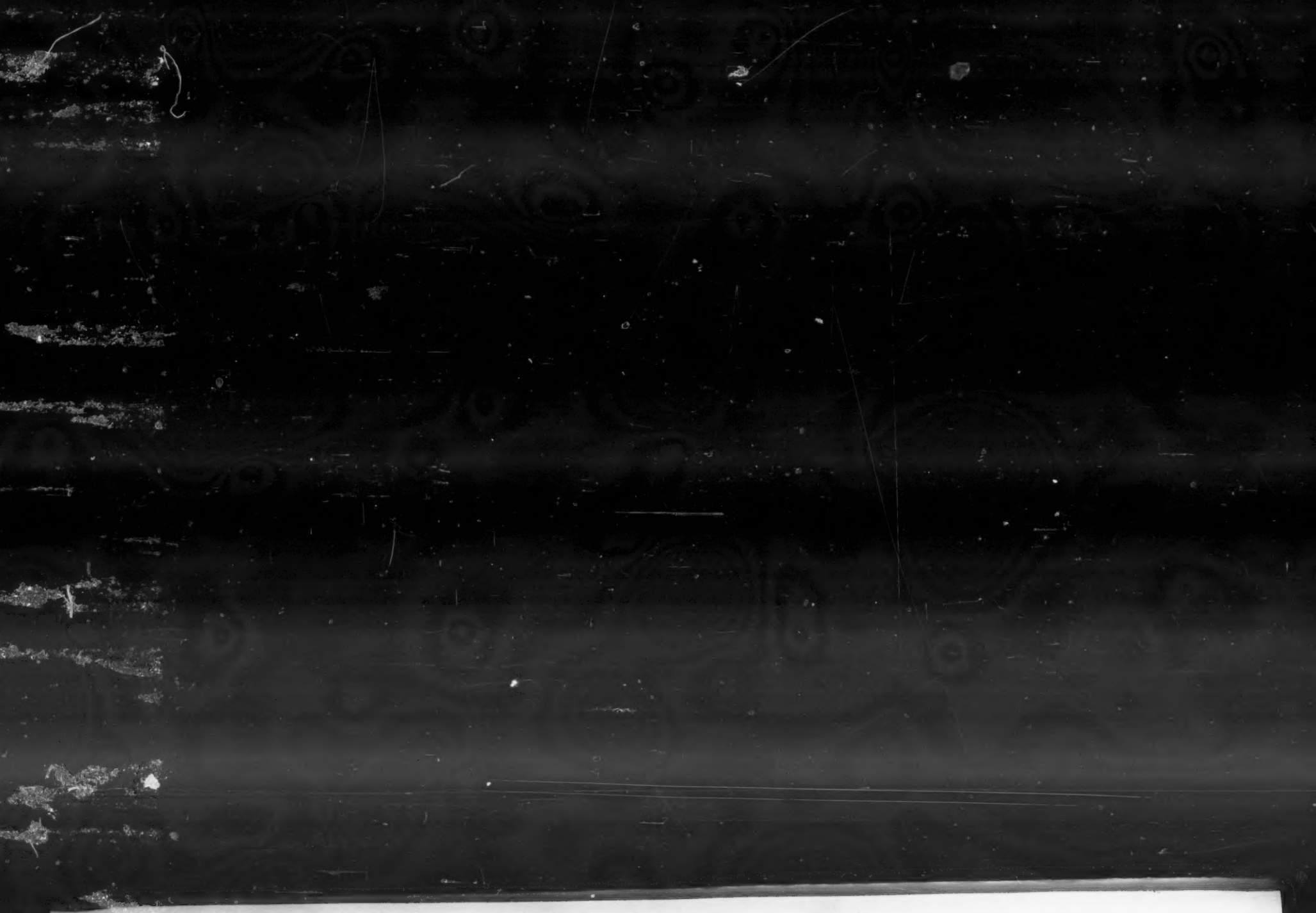
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